

From the Frying Pan into the Fire

MR WILLIAM RUCKELSHAUS'S decision to override the decision in May of his own examiner and to commend to Congress what is for practical purposes a total ban on the use of DDT in the United States is an assault on reason comparable with the decision in October 1969 to ban the use of cyclamates in the United States. By all appearances, Mr Ruckelshaus has bowed to the popular clamour against DDT and, although there is no immediate prospect that American manufacturers will be prevented from exporting the pesticide to developing countries elsewhere, there is now a danger that other countries will follow the lead of the United States without fully counting the cost that will be involved. Worse still, the way in which Mr Ruckelshaus has reached his abrupt decision without fully taking account of the orderly legal processes which his agency has devised will confuse and tend to make irrational future decisions on issues like this.

In January 1971, the Environmental Protection Agency gave notice that it had in mind a total ban on DDT and related pesticides, thus extending the regulations on use which had been introduced in the previous two years in the United States. The immediate result was a series of legal objections (as prescribed by law) from chemical manufacturers and agricultural interests and (as prescribed by law) the luckless Edmund M. Sweeney was appointed examiner for a public hearing lasting seven months. By all accounts, the proceedings themselves were replete with minor farce. One witness who described horrendous concentrations of DDT in the marshland soil of Long Island was discomfited eventually to have to admit that his samples had been taken from a place where a DDT spraying truck had been loaded and unloaded. The crude calculations of the National Academy of Sciences committee (*Chlorinated Hydrocarbons in the Marine Environment*, NAS, 1971) which alleged that a quarter of all the DDT ever manufactured has already found its way into the oceans were at long last publicly discredited.

But the hearings also provided a public platform for the opposing views on DDT at the end of which Mr Sweeney, not in his manner conspicuously the most judicial of public examiners, declared that neither Mr Ruckelshaus nor his cheer leaders, principally the Environmental Protection Fund, had proved the case that the hazards of continuing to use DDT outweighed the benefits. Mr Ruckelshaus, as is his right had also appointed a scientific advisory committee which, with the same facts, has come to the opposite conclusion. In the circumstances, it is inevitable that there will be widespread confusion about the rights and wrongs of this tortuous issue. It is a great misfortune that it has now been settled, apparently for good and all, in such a heavy-handed fashion.

For countries other than the United States and those in western Europe, the most conspicuous benefits of DDT and similar pesticides are in public health, and the cam-

paign against malaria is a monument to what has been done in twenty years to control potentially dangerous mosquitoes. It is something to be grateful for that Mr Ruckelshaus has made the token gesture of keeping DDT on the list of materials that may be used in public health—a token measure in the United States (see page 422). In the United States, two-thirds of the DDT at present used finds its way into agriculture, and three-quarters of that is thought to be used in protecting cotton crops against the bollworm and the boll weevil. In the past few years, the acreage of cotton treated with DDT has declined to 35 per cent of the total planting, as organophosphorus pesticides such as parathion have been more widely used, but there is no doubt of the potential value of pesticide treatment of cotton. The Senate committee on government operations quoted figures in 1965 to show that treatment with DDT could be relied upon to increase the yield of cotton from a crop by more than 50 per cent. Since then, the cost of pesticide treatment has increased to more than five cents per pound of cotton produced, a substantial fraction of the selling price, but at the same time a measure of the importance of pesticide treatment in this kind of agriculture. Mr Ruckelshaus says in his report supporting his decision that DDT should now be banned that there is no reason why the ready alternative to DDT, parathion, should be more expensive, and that there is even some evidence that the trend will go the other way. This, however, remains to be demonstrated and it is beyond dispute that the control of insects such as the boll weevil by direct biological intervention is not merely a long way round the corner but hypothetical as well. In short, in spite of the evident health of the agricultural industry in the United States, the decision to ban DDT, soon to be ratified by Congress, will entail a considerable economic penalty.

What will be the benefits of the decision? In the past several years, it has become apparent that the chief argument against the continued use of DDT and the other persistent pesticides is that they may cause damage to wild life. The advisory committee which reported to Mr Ruckelshaus last November made this the chief plank of its recommendations that steps should be taken to continue and even to accelerate the decline in the use of DDT in the United States since the mid-1960s. It is only fair to say, however, that the evidence that DDT can damage wild life, while suggestive, is so far only circumstantial. Laboratory experiments have shown that fish such as salmon containing five parts per million of DDT are comparatively infertile, but there has so far been no evidence that such declines in wild fish populations which have been observed can be attributed to pesticides or can be weighed in the balance against the depredations caused by over-fishing. To be sure, there are some places—Lake Michigan is a conspicuous example—where the residues of DDT are already so great that commercial fishing has been made unproductive, but the trend of recent years in the consumption of DDT has been downwards, even in



the United States—and, ironically, there is no reason to believe that a ban on the use of DDT will bring about a more rapid decline than would, for example, a sensible restriction on continued use.

This is why most students of the problem have come to the conclusion that the chief victims of DDT so far are likely to be birds, both predatory birds such as eagles and falcons and fish-eating birds, especially the pelicans off the coast of California. Over the years, a good deal of evidence has accumulated to suggest that eggs containing large quantities of DDT, and which are presumably laid by birds with a similar disability, have thinner shells and are therefore less viable than they would normally be. Although the evidence for a logarithmic relationship between dose and response (the percentage of eggs which hatch) was challenged during Mr Sweeney's public hearings, and although attempts to replicate the effect by feeding DDT to hens have so far been unsuccessful, it is probably wise on balance to suppose that DDT is actually bad for individual birds. It does not of course follow from this that the decline in bird populations is entirely attributable to the production of the new pesticides in the past 20 years—other environmental factors, especially the increasing occupation of uncultivated land by human beings and their equipment, may also have played a part in reducing the numbers of peregrine falcons and hawks. The pelicans off the coast of California are probably, however, an identifiable case of a bird population which has been harmed by pesticides. One unhappy feature of Mr Ruckelshaus's judgment in the case of DDT is that it does not face directly the question of what price should be paid for the preservation of this restricted population.

Mr. Ruckelshaus's most serious error, however, is to have given public and official recognition to the belief that DDT and other persistent pesticides are, possibly remotely, a carcinogenic hazard. Ever since Rachel Carson, this has been a contentious issue. There are few who now believe Miss Carson's biochemical speculation designed to show that the persistent pesticides would tend to cause cancer by creating a hormonal imbalance. Since the early 1960s, however, there have been several series of experiments designed to test this alarming hypothesis, using mice and more recently rats. These have given ambiguous results. For one thing, there are doubts about the reliability of extrapolating from strictly inbred strains of laboratory animals, with their idiosyncratic tendencies to carcinogenicity, to human beings. In any case, the most suggestive signs so far uncovered have been occurrences of the apparently benign liver tumours called hepatomas in small proportions of laboratory mice fed with doses of DDT as great as 300 milligrams a day. It must be openly acknowledged that professional opinion is divided on the question whether hepatomas are early stages in the development of malignant tumours, yet Mr Ruckelshaus does not acknowledge as much. His strongest argument is merely that in circumstances in which there is the possibility of risk, however remote, and an alternative pesticide which can be used in present circumstances, it is better to ban DDT and to settle for parathion instead. It would have been more open to have said that the chief evidence so far is that there is a possibility that bird populations may be damaged.

The most unfortunate aspect of the decision is that it has lost an opportunity to make an altogether more rational decision. The case against DDT and its chemical relatives has never been absolute. On one side of the

argument have been those who attempt to calculate the potential hazards of continued use and who acknowledge that the calculation is at once indefinite and liable to error. On the other side have been those who draw attention to the agricultural advantages of DDT in advanced societies such as the United States and who are more able to quantify the results. In circumstances like these, however, it would seem that the interests of both parties to this continuing controversy would have been met more adequately by a further restriction of the use of DDT and the persistent pesticides, not by a total ban. After all, much of the present fuss would not have arisen, and pesticide residues would not have accumulated to the extent they have in human fat, if the agricultural uses of the persistent pesticides in the past twenty years had been more prudent. So might it not have been possible for Mr Ruckelshaus to have settled for restrictions on the intensity with which these pesticides are used? Might not the same objective have been achieved more easily if he had slapped a tax on them—and used the money raised to sustain the programme of careful monitoring, still urgently necessary, that would have thrown much needed light on a tedious controversy occupying the past several years? In short, his present decision is not merely a bad example for nations elsewhere and a deprivation of American agriculture of an important degree of freedom but a bad precedent for the future, when the need to balance intangible risks against benefits which are almost as intangible will no doubt proliferate.

Mr Strong's Recipe

THE outcome of the Stockholm Conference on the Human Environment has been as cheerful as could have been expected. To be sure, the last few days, at the end of last week, were enough to make even diplomats bite their nails, waiting to see whether the Chinese demand that the Declaration on the Human Environment should be re-examined would prove to be subversive or constructive. In the event, it made very little difference, even if the draft declaration now embraces even more topics with no connexion with environmental questions than did the original version. The truth is that the declaration is an expression of good intentions which, like the Declaration on Human Rights, will be observed only in that great utopia when nations sink their differences in mutual accord and when governments put the public interest before the opportunity for injustice. The most practical result of the conference, therefore, is the decision (yet to be ratified by the General Assembly of the United Nations in November) that there should be a permanent secretariat to coordinate the specialized activities of the United Nations and a fund of money, yet to be determined, to finance the work. No doubt the indefatigable Mr Maurice Strong, the secretary general of the Stockholm conference, will be in charge. His immediate problem will be to reconcile the specificity of the recommendations that have been approved in Stockholm, and their ambitious scope, with the need to cut the coat to suit the cloth and to tackle first those problems which are most amenable to solution.

But has not Stockholm changed the mood in which nations approach environmental problems? There is some truth in this assertion though not precisely that which the enthusiasts now claim. For one thing, the conference

has served not so much as a rallying point for those who espouse the new fad of zero economic growth but rather as a platform for those who insist that environmental problems are not soluble unless more resources are available, that there is in any case no necessary conflict between economic growth and the careful management of the environment, and that, in any case, the most serious environmental indignities are not those of pollution, however international, but those of poverty, disease and unjust government. This is the point that Mrs Gandhi, the Prime Minister of India, made when she reminded the delegates at Stockholm last week that in India the environmental problems first to be solved are those that afflict the millions of people living on the pavements of Calcutta and Bombay. But the mood of governments may also have been changed by the insistence of the developing countries that economic development is for them a more urgent cause than the preservation of the environment. Nations elsewhere should take this lesson to heart. The developing countries are neither feckless nor short-sighted. The truth is that if what advanced societies hanker after is a decent environment, they must first set out to create a decent world. This will not be possible so long as they remain as mean and short-sighted as they were at UNCTAD at Santiago six weeks ago.

Academic Roulette

PROFESSOR EDWARD NEVIN has started some troublesome hares in an article in the current issue of *Economic Journal* (82, 658; 1972) with the title "How Not to Get a First". The raw materials of this subversive study are the records of British universities showing the proportions of first graduates awarded honours degrees of various distinctions. (Readers elsewhere should know that undergraduates following honours degree courses, if successful in their final examinations, are lumped by their examiners into four categories, classes I, II-1, II-2 and III. A man or woman with a first-class degree walks tall; a third-class person usually spends his time telling his employers of his activities with the university campanologists and the like.) Because of the way in which degrees are labelled and because of the potential value of particular classifications to individual careers, there has in the past few years been a steady rumble of concern among students and teachers about the differences of practice between different universities and between different faculties within the same university.

Professor Nevin's analysis confirms the common suspicion that universities differ markedly in the generosity with which they award distinctions to first graduates. In pure science subjects, for example, the percentage of first and upper second honours degrees awarded by British universities between 1966 and 1969 ranged from 32.1 per cent at the University of Essex to 59.7 per cent at the University of Kent. In the social sciences, a student's chances of picking up a distinguished degree are even more a matter of pot luck. The University of Wales Institute of Science and Technology seems to have been exceptional in awarding only 8.9 per cent of first and upper second degrees to students reading social sciences between 1966 and 1969. Elsewhere, the corresponding percentage appears to have ranged from 22.5 per cent (at the University of Bradford) to 70.7 per cent at the University of

Kent (evidently the university most anxious to give its young men and women a good start in life). At the University of Cambridge, examiners are more fierce—the percentage of students in pure science emerging in the two upper classifications of examination lists was 37.8 per cent, compared with 34.2 per cent in the social sciences.

Why should there be such variations between different universities? On the face of things, there is nothing in the figures to suggest a general rule. The hypothesis that newer universities which have grown quickly, or departments which have grown quickly, may contain unusually large proportions of young people among the teaching staffs, and that they might on that account be wantonly mean to their students, is contradicted by the observation that the newer universities tend to be found at the top and the bottom of the percentage tables. So is it possible that the variations now identified spring from objectivity among examiners and reflect a variation of the quality of university entrants or of the weeding out process which precedes examinations? That conclusion would bring joy to those who hold that university entrance procedures, based as they are on the performance of intending students in A-level examinations, are inherently faulty. But more sceptical analysts will point out that it is unreasonable to suppose that autonomous boards of examiners, recruited in the way which has become familiar in British universities, will be anything like as consistent.

How disturbing is all this? The first thing to be said, of course, is that the class of the degree which a student is awarded is often strictly irrelevant to the question of his suitability for the particular jobs for which he may afterwards apply. In Britain, employers such as the Civil Service have long recognized the truth of this simple proposition—they hold their own examinations. Equally, academics selecting potential research assistants do so on the basis of a personal assessment of a student's flair for research (which is not to say that this system is entirely free from nepotism and a tendency to perpetuate the prejudices of university teachers in research). And discriminating employers are increasingly inclined to follow the same tack, suiting people as far as possible to the jobs which they might do. For all these reasons, the attempt by university examiners to wield Occam's razor once a year is increasingly of interest only to themselves.

100 Years Ago



Spectrum of Lightning

I HAD a good view of the spectra of lightning during the storm of yesterday. Frequently there was only one bright line visible, this being coincident with the nitrogen line. At other times there were several bright lines, sometimes with, and at other times without, the nitrogen line. Several flashes showed a continuous spectrum without visible lines. My instrument was a small direct-vision spectroscope, but sufficiently powerful to divide the sodium line.

J. P. JOULE

Broughton, Manchester, June 19

From *Nature*, 6, 161, June 27, 1872.

OLD WORLD

Is DDT Carcinogenic?

As Mr William Ruckelshaus, director of the United States Environmental Protection Agency, laid the environmental lobby in America to rest last week by banning most uses of DDT throughout the country, he raised again the old spectre of DDT being carcinogenic.

The argument by now is an old and hoary one, but whatever future research may show, there is no evidence to date that the chemical causes cancer in man, although it is clear that it does accumulate in the fatty tissues of the body, apparently without any harmful effects.

The medical evidence against DDT comes from studies in mice which develop lesions in the liver when fed levels of DDT ranging from 10 to 250 ppm. Work at the International Agency for Cancer Research in Lyons, partly financed by the World Health Organization, is confirming these findings, but they are a far cry from proof of carcinogenicity in man. Only certain strains of mice develop the lesions. Rats treated the same way may produce lesions, although this is not yet clear. The World Health Organization is financing work in Moscow on rats, but studies have not yet proceeded far enough to produce results.

Equally, the value of studying the type of lesions produced in mice has been called into question recently by Grasso and Crampton (*BIBRA Bulletin*, 11, 3; 1972) and by Rowe and Grant (*Intern. J. Cancer*, 6, 133; 1970). Some strains of mice which have been used for testing the carcinogenicity of DDT have a tendency to form lesions of the liver which calls into question the value of studies on mice. Equally the types of lesion found in mice are not comparable with any found in man.

But if the evidence gained from mice remains unconvincing, results from epidemiological tests so far are completely negative.

The World Health Organization has such studies running in Brazil, Israel, the United States and India among other countries, and there is no evidence that the DDT levels found do cause cancer. Studies at DDT manufacturing plants where workers' blood levels can be anything between 50 and 100 times the "normal" levels found, show no evidence of an increased incidence of cancer, and studies over a 14-year period at one of Shell's manufacturing plants where dieldrin—a close relation of DDT—is made, produced equally negative results, although at very high blood levels there were small bio-

chemical changes in humans, insufficient, however, to affect the subject's well-being.

The position seems to be adequately summarized by the 1970 annual report of the International Cancer Agency, published this week, which states that studies of the carcinogenicity of DDT in experimental animals "have shown that, at very high doses, liver tumours are produced in mice. In other studies, the levels of DDT stored in human fat tissues, sampled from different populations, are being measured; although these levels are often very high there is as yet no epidemiological evidence of any modification of the cancer pattern in any of the populations studied".

Clearly DDT cannot yet be given a completely clean bill of health. Possibly the lesions in mice are in fact significant, and equally really long-term epidemiological studies of the sort that the WHO is currently running may yet reveal that DDT has a tendency to

cause cancer over long periods, but to date there is no basis for Ruckelshaus's statement.

Will Britain follow the United States in the ban? In spite of speculation that other developed nations will follow the United States down its pioneering, if possibly unwise road, it seems unlikely that Britain will do so immediately. Mr Ruckelshaus said in London this week that he has had talks with the Department of the Environment on the subject and that he will be sending the British Government the 36-page document on which the EPA based its controversial decision, but the reaction among British scientists in the field is cool. One described the United States action this week as "selfish" in that its decision is likely, whether the United States is willing to admit it or not, to coerce nations that cannot yet afford to manage without DDT to ban the chemical.

There is no doubt that Europe and

SPACE

Onward with Europa

THE ELDO council has now agreed to release a further \$4.8 million for work on the F12 launcher in the Europa II series. This money had been allocated in the 1972 budget but was frozen after the disastrous F11 launch in November 1971.

This decision, taken by the council, seems to prejudge the issue to be debated at the meeting of the ELDO ministers in Brussels on July 11 on whether work should continue on F12. The confidence of the ELDO council that the ministers will approve a continuation of work on Europa II is no doubt based on the report of the causes of the failure of F11, which broke up after 150 seconds of flight.

The abortive launch of F11 was, according to the report presented to the council, the result of a computer failure which was itself caused by a "manifestation of electromagnetic interference aggravated by the fact that digital equipments susceptible to interference and relatively unprotected (the guidance computer and third stage sequencer) had been placed in an unfavourable electrical environment".

In view of this report ELDO has taken action to prevent such occurrences in future—the technical side has been strengthened and, more important, ELDO said last week that "the organization, timescale and finance to guaran-

tee proper reliability of the Europa II vehicle" has been improved.

The ELDO council also made plans for the future launches of Europa satellites. It is planned that after F12, which is now scheduled to be launched between May and November 1973, provided the ministers agree next month, F13 will be launched in late 1973 or early 1974. If it is decided to go ahead with these launches then the cost will be between \$21 and \$26 million. The Symphonie satellites will then be launched by F14 and F15 during 1974, whereas F16 is to be used for ESRO's COS-B satellite.

There are no definite plans for F17 and F18, whose construction has yet to be approved, but the council decided to open negotiations with the Symphonie group and with ESRO for the sale of these satellites.

Another decision which will face the ELDO ministers next month will be the future of the Europa III launcher. This launcher is to be more powerful than Europa II and is designed to put a payload of 750 kg into a geostationary orbit. This launcher is to be a two-stage rocket whose development is estimated to cost \$470 million. One of the features of the launcher, which particularly concerned the ELDO council at its meeting, was the possibility of making the second stage compatible with the space tug.

the United States with their advanced technologies and the absence of malaria can manage without DDT, but whether many poorer parts of the world can yet do so is another question. The World Health Organization and the Food and Agriculture Organization of the United Nations will continue to recommend that where suitable substitutes are not available DDT should continue in use.

STEEL

Refurbishing Old Dreams

BRITAIN'S steel industry may not be too sure where it is going, but at least it can now see where it has come from. The iron and steel gallery at the Science Museum was reopened last week after eighteen months, and traces the history of the iron and steel industry from pre-historic times, including in its sweep the manufacture of Eskimo knives from meteor iron and the latest in basic oxygen steelmaking processes.

Refurbished at a cost of more than £20,000, the gallery includes several new historical exhibits, many of which have long been hidden in the reserve collections. The new setting is resplendent with modern stainless steel.

The gallery is now an attractive but logical display. There are models of the original Bessemer process of 1856 and models of modern steel plant. Giant photographs of the Firth of Forth steel bridge of 1883 and of the steel rails laid at Derby in 1857 adorn the walls, and a giant Bessemer converter, installed at Barrow-in-Furness in 1864, dominates the entrance to the exhibition. Various manufacturing processes from wire stretching to centrifugal casting are also on display, while part of one wall is black with the giant size of two open hearth furnaces side by side, a model man dutifully in attendance.

The museum also has plans to re-display its metallurgy section, the new sections to link with the gleaming iron and steel gallery.

METEOROLOGY

Watch Unkept

THE prospect that the World Weather Watch will be delayed by lack of trained staff was one of the points made by Dr B. J. Mason, director general of the UK Meteorological Office, during the sixth annual Aslib lecture last week. The prospect now is that the first stage of the programme, consisting of the establishment of meteorological stations around the world, will not be completed until 1975, two years later than originally planned. This immediate objective, intended to improve the quality of meteorological observations from parts of the world in which meteorological stations are thinly scattered, would have

required the World Meteorological Organization to foster the establishment of 40 new meteorological stations and to improve the equipment at a further 70 stations. According to Dr Mason, the chief difficulty so far has been to find staff to run some of the outlandish stations, particularly those in developing countries.

The world-wide communications system is, by contrast, well advanced and Dr Mason thinks it should be largely operational by the end of this year. Ultimately, the World Weather Watch calls for a world-wide network of meteorological stations not more than 500 kilometres apart on land and not more than 1,000 kilometres apart at sea. When it is complete, the network should bring about a remarkable improvement in the quality of weather forecasting. Dr Mason was also cheerful about the prospects for the Global Atmospheric Research Programme (see *Nature*, 233, 382; 1971). The plan to make a detailed study of 1,000 kilometres square off the west coast of Africa is well advanced, and the team of scientists likely to be involved is being assembled at the Meteorological Office in Bracknell. That exercise, Dr Mason said, would be a necessary foundation for the success of the First Global Observing Year planned for 1976. Plainly, however, it is more difficult to provide a timetable for that component of the Global Atmospheric Research Programme which aims at providing numerical weather forecasts. At Bracknell, they are now working with a ten layer model, but it remains to be seen whether this will be a sufficient improvement on previous more simple models to make weather forecasting an objective science.

EDUCATION

Comprehensive Schools

A REPORT which debunks some of the popular myths of comprehensive education was published recently. The report, *A Critical Appraisal of Comprehensive Education* (NFER, £3.25), is the third part of a trilogy commissioned by the Department of Education and Science at a cost of £180,000 to seek out the truth about comprehensive education.

Among the educational dragons that this report purports to slay are the belief that high fliers are held back by their slower classmates in comprehensive education (they are not), that comprehensives cannot supply good sixth form courses (they can, even when they have more than their fair share of less able pupils), and that large schools isolate children (they do not).

The 240-page report took two years to hatch, and its principal conclusions

are based on a detailed study of 12 comprehensive schools in selected parts of England and Wales. 2,270 pupils and 504 teachers were involved, and the study is the largest in-depth study of comprehensive schools yet undertaken.

There is little doubt that the findings of the National Foundation for Educational Research will not quieten the fervid opposition to comprehensives in some parts of Britain, but the foundation's findings, because they are the result of detailed study, may well have real significance, although the foundation itself is the first to point out that the results cannot be taken as representative of comprehensive schools as a whole.

Not that everything in the comprehensive garden is rosy. The report has some unpleasant findings about pupil/teacher ratios. Pupils taking CSE courses get fewer teacher resources than more able children, or, for that matter, than less able children, which, as the report points out, can "hardly encourage these average pupils to continue their formal education". Equally the report declares that whereas no more middle class children are found in upper streams than their ability would warrant, 25 per cent of working class children were in the wrong stream and a greater proportion of these were underplaced than middle class children.

Comparing the standards of the sixth forms in the schools studied to the national average, the report concludes that their sixth form records were average or above, but that their examination records were average or below. The report adds, however, that given the characteristics of the pupils at the twelve schools, their "examination standards appear satisfactory". Strangely, the report has remarkably little to say about university and college entrance.

Aharon Katchalsky Memorial Fellowship

SEVERAL expressions of support for this scheme have been received from *Nature* readers. The Weizmann Institute itself is now working out practical arrangements. It is intended to form an international committee and further details will be announced after a symposium linked with Katchalsky's work due to be held at Rehovot next week.

In the meantime, those wishing to contribute to the fund which will eventually be established in Israel should send contributions to the Secretary, Weizmann Institute Foundation, Rex House, 4 Regent Street, London SW1.

NEW WORLD

DDT Condemned

by our Washington Correspondent

MR WILLIAM D. RUCKELSHAUS, Administrator of the Environmental Protection Agency, last week hammered what could be the final nail into the coffin of DDT in the United States. After three years of court actions, public hearings and at times an acrimonious scientific debate, Ruckelshaus has decided that "the long-range risks of continued use of DDT for use on cotton and most other crops is unacceptable and outweighs any benefits". Accordingly, he has slapped almost a total ban on the use of DDT in the United States after December 31 this year.

The decision to ban DDT was immediately greeted with two court actions—one attempting to get the ban repealed and the other asking that it be put into effect immediately—but the battle over the pesticide is probably now all over bar the shouting. Five scientific committees in almost as many years and three court decisions have recommended that the use of DDT be phased out as quickly as possible. Against that background, it is highly unlikely that the ban will be overthrown by the courts, even though the manufacturers have filed their appeal in New Orleans, in the heart of the cotton belt. DDT, the pesticide hailed in the 1940s and 1950s for its remarkable successes in combating malaria, typhus and other insect-borne diseases, therefore seems destined to become a monument to the power of the environmentalist movement in the United States.

When the ban comes into effect at the end of the year, the only uses of the pesticide that will be allowed in the US will be for public health service programmes, for quarantine and for prescription drugs. Since DDT has not been used for public health programmes for several years, however, his exemption from the ban is largely symbolic and is designed chiefly to offset a panic reaction by other countries. If the United States maintains the option of using DDT for its own public health programmes, the argument goes, then other countries, in which DDT plays a vital role in disease control, will be less disposed to ban it themselves. Exports of the pesticide from the United States are not affected by the ban.

Mr Ruckelshaus has delayed bringing in the ban on DDT until the end of the year to give farmers sufficient time to learn how to apply methyl parathion, the pesticide which will probably be

used as a substitute. Methyl parathion, while acutely toxic, is rapidly degraded in the environment, and will therefore not produce such a long-lasting environmental effect, and it will not be so easily transported to remote regions. But the Environmental Defense Fund, the environmentalist group that has filed suit to make the DDT ban effective immediately, believes that there is no need for a training period, and that the damage wrought to the environment by DDT is so great that the pesticide should be banned immediately.

To back up its suggestion that no training period is required, the EDF points to the fact that DDT is almost invariably mixed with methyl parathion when it is applied to cotton, so that cotton workers are already sufficiently acquainted with the pesticide. The case for an immediate ban is, however, somewhat damaged by a considerable body of evidence which suggests that the environmental burden of DDT will decline only slowly even after a total ban on the pesticide. A study carried out at Oak Ridge National Laboratory, for example, suggests that it will take between 15 and 20 years for the amount of DDT in human tissue to decline to half its present level, even if no more DDT is pumped into the environment. Six months' delay is therefore unlikely to present much additional hazard.

With the reports of five scientific committees, decisions from three federal courts and a wave of public sentiment to back him up, it would seem that Ruckelshaus had an easy decision to make. But it is not that simple. For one thing, a protracted public hearing on the risks and benefits of using DDT, which lasted for seven months and produced nearly 10,000 pages of evidence, ended in April this year with the recommendation from the hearing examiner that the pesticide should remain in use. Moreover, scientists are strongly divided on the question of whether or not DDT poses a risk to human health, and although no pesticide has been studied more intensively than DDT, there are still yawning gaps in the knowledge about its effects. The whole debate over the risks and benefits of using the pesticide, in fact, provides an interesting case study in science and public policy.

In step with the rising concern about the effects of DDT, but partly reflecting the fact that new pesticides had come on the market, use of DDT in the United States dropped dramatically during the 1960s, from about 79 million

pounds in 1959 to just under 12 million pounds in 1970. But the first attempts by the federal government to curb use of the pesticide did not come until 1969. In that year, Mr Clifford Hardin, then Secretary of Agriculture, banned use of DDT on tobacco, for treating Dutch elm disease, around the home and over water, but he left untouched the chief use of DDT in the United States—treating cotton.

Hardin's decision to ban some uses of DDT was prompted by a court action brought by environmentalist groups led by the Environmental Defense Fund, but the exemption of cotton and some other minor uses of DDT from the ban (cotton farming accounted for some 86 per cent of DDT use last year) was appealed against by the organization. At that point in the process, responsibility for regulating pesticides was transferred from the Department of Agriculture to the newly created Environmental Protection Agency, which has proved itself to be remarkably tough in enforcing its Congressional mandates. The Environmental Defense Fund won its appeal in court, and in January last year Ruckelshaus duly obeyed the court decision by cancelling all the remaining uses of DDT.

The Federal Insecticide, Fungicide and Rodenticide Act, the legislation which sets out the administrative procedures to be followed when registration of a pesticide is cancelled, provides an opportunity for manufacturers to appeal against the ban by calling for independent review of the decision by a scientific advisory committee or a public hearing. While such a review is taking place, the manufacturer is able to continue marketing the pesticide. Manufacturers and formulators of DDT in the United States made to appeal against the ban by calling for both a scientific review and a public hearing, which came up with broadly similar findings but conflicting recommendations.

In many respects, the reports of the scientific advisory committee, and of the public hearing examiner, and the opinion published by Ruckelshaus with his cancellation notice last week, provide illuminating examples of how the same set of facts can be interpreted in different ways to arrive at different policy decisions. Some examples taken from the three reports serve to illustrate the different emphasis placed on the facts.

As far as damage to aquatic life is concerned, for example, Mr Edmund

M. Sweeney, the public hearing examiner, finds that as a "finding of fact", DDT "can have a deleterious effect on freshwater fish and marine organisms when applied directly to water" and that "the theory of biomagnification would seem to be adequately demonstrated in the case of fish, giving rise to concern over use of pesticides with a persistence such as DDT". Similarly, the scientific advisory committee, which met under the chairmanship of Dr James Hilton of the University of Texas and which issued its report in September last year (see *Nature*, 233, 299; 1971), concludes that "there is sufficient toxicological

information on DDT in aquatic species to indicate that reduction and prevention of contamination of water sources is a problem of major concern", and Mr Ruckelshaus concludes that "the evidence presented by (the EPA's) Pesticides office and the intervenors, EDF, compellingly demonstrates the adverse impact of DDT on fish and bird life".

Nevertheless, Sweeney argues that the pesticide has found its way into water in the past chiefly through misuse, and concludes "while it is necessary to maintain a vigilant concern over the possibility of serious damage to our important aquatic life, it is questionable whether the evidence presented in this case supports a finding that, at present and foreseeable future levels, the use of DDT would cause damage to aquatic life sufficient to justify complete cancellation". Ruckelshaus, on the other hand, argues from the same body of facts that the manufacturers' "assertion that there is no evidence of declining aquatic or avian populations, even if actually true, . . . does not refute the basic proposition that DDT causes damage to wildlife species".

The question of whether or not DDT is a carcinogen provides the starkest difference of opinion between Sweeney on the one hand and Ruckelshaus and the scientific advisory committee on the other. The manufacturers of DDT argued in the public hearing that animal studies have so far not been able to prove that DDT is carcinogenic, and although Sweeney acknowledges that there is "no showing of any evidence that man himself is not safe from cancer from the present dosages to which we are exposed", he continues, "really, it can't seriously be contended that the fact that DDT has NOT been proven NOT to be carcinogenic in man, is a logical basis (*sic*) for advocating a complete ban on all future uses of DDT".

The scientific advisory committee, on the other hand, while admitting that "the possibility of . . . carcinogenesis is low", argues that "the evidence (from animal studies) to date clearly shows that DDT induces hepatomas and suggests that it may be carcinogenic". And Ruckelshaus argues that although there is no evidence of carcinogenicity from limited studies of workers in DDT manufacturing plants, the data from animal studies indicate that "DDT presents a carcinogenic risk". In short, Ruckelshaus has accepted that the doubt is great enough to call for a ban, while Sweeney suggests that until there are more convincing data available, a ban on DDT is not justified. So far, the courts have agreed with Mr Ruckelshaus and there is little likelihood that there will be a change of heart.

NATIONAL SCIENCE FOUNDATION

The Axe Falls

by our Washington Correspondent

It is now certain that the National Science Foundation will have less money to spend next year than it had bargained for. Last week, the Senate followed the lead of the House of Representatives by voting to give the foundation some \$650.2 million to spend in the 1973 fiscal year. The money is made up of \$619 million in new appropriations and \$31.2 million left over from previous years. The foundation's plans require expenditures of \$674.7 million.

The NSF's budget is contained in a bill appropriating money to several agencies, which was passed last week by the Senate and last month by the House of Representatives. Although the bill must go to a conference committee to iron out some differences of opinion between the House and the Senate, the figure is no longer in doubt, since both agree on the total funding for the foundation. One aspect of the budget which must be agreed on, however, is the proportion which is earmarked for science education and graduate student support. The House of Representatives has instructed the NSF to spend a greater proportion of its budget on these activities than has the Senate.

Although the appropriations bills do not tell officials of the foundation where they should apply the knife, it is clear from the report of the House Appropriations Committee, which was responsible for recommending the budget figures to the rest of Congress, which portions of the foundation's activities it would like to see trimmed. The report states: "A new emphasis has developed in the National Science Foundation programmes in recent years. This appears to put more emphasis on techniques and methodology and less emphasis on fundamentals and substance. The often expressed concern of knowledgeable individuals that the foundation may assume the role of directing instead of supporting research in our nation appears to be evolving in the RANN program, and in other new approaches that are proposed in the budget. . . . The Committee is concerned that this new support and promotion of short term goals is indirectly cutting into support of established and basic programs, such as institutional and graduate student support."

CHRONOMETRY

Absolute Time?

YET another adjustment in radio time signals will be made at midnight on June 30, a consequence of the changeover to atomic time as a basis for international time keeping on January 1 of this year.

Greenwich Mean Time is based on the diurnal rotation of the Earth and because the Earth is slowing down at the rate of three thousandths of a second a day, the second based on GMT is not sufficiently accurate for several scientific purposes.

Uniform time is obtained from atomic clocks which were standardized by being made to correspond to GMT in the year 1900 but absolute atomic time now differs from GMT by ten seconds. The change on June 30 will add another second to this difference.

There is an agreement that the time signals based on atomic clocks, will not be allowed to diverge greatly from GMT, but since January GMT has increasingly diverged from the signals based on atomic time, so that the difference now is between 0.6 and 0.7 seconds. To bring the two time scales closer together, radio time signals everywhere will be retarded by one second on June 30—thus making the relative difference between GMT and the time signals 0.3 to 0.4 seconds, a time difference that will now decrease as the Earth continues to slow down.

According to the Royal Greenwich Observatory it might be necessary to carry out another adjustment at the end of 1972 but this can not be accurately predicted because of the uncertainty of the slowing down of the rotation of the Earth.

HEALTH RESEARCH

Bandwagon Rolls On

by our Washington Correspondent

ONE effect of the crusade against cancer that swept through Congress last year is likely to be a bonanza for all kinds of health research. In an atmosphere reminiscent of the early 1960s, when Congress was intent on building up the National Institutes of Health (NIH), committees on Capitol Hill are pushing for huge increases in funding to help combat the major diseases that kill millions of Americans each year. Sickle cell anaemia and diseases of the heart and lungs have already been singled out for crusades of their own (see *Nature*, 234, 377; 1971, and 236, 93; 1972), and the House Appropriations Committee has now extended Congressional largesse to many other areas of health research.

Calling President Nixon's budget for the National Institutes of Health "a feeble gesture" and "disappointing", the committee has recommended that Congress should add nearly \$143 million to it. The committee also believes that the National Cancer Institute and the National Heart and Lung Institute should each get a 30 per cent increase in their budgets compared with this year, and has accordingly given them extra helpings of \$60 million and \$45 million respectively, on top of the money requested in the Administration's budget.

The House Appropriations Committee's recommendations are all the more surprising because it is traditionally the more conservative of the two Congressional appropriations committees, usually recommending smaller budgets than its counterpart in the Senate. Overall, the committee has added \$912 million to the Administration's request for the Departments of Labor and Health, Education and Welfare, and with the likelihood that the Senate committee will be even more generous, there is a possibility that President Nixon may veto the bill when it is finally passed by Congress. That happened in 1970, when Congress added \$1,200 million to the appropriations request, but the exigencies of election year may yet ensure that NIH will get the money it hopes from Congress.

The appropriations committee was particularly irked by the fact that the Administration's budget would have cut the funding for new research projects in institutes of NIH other than Cancer and Heart by 10 per cent, compared with funding for this year. The committee was "amazed" at the cut, and pointed out that it would "quickly stultify research". It added funds to each of the institutes so as to restore the number of research grants that can be awarded to the 1972 level.

As for the National Cancer Institute, the committee recommends that it should be given \$492.2 million in 1973—\$113.4 million more than it has received this year, and \$60 million more than the Administration requested. The increase is justified on the grounds that "eminent scientists, who testified before the committee, and the Director of the Institute himself, indicated that more funds could be very effectively used". That, in itself, is a remarkable indication of the Congress's commitment to the cancer crusade. Singled out for mention in the committee's report are the chemotherapy programme, research into the chemical causes of cancer and the cancer control programme, all of which are recommended for their fair share of the institute's increased budget.

The increase suggested for the National Heart and Lung Institute would bring the institute's budget to \$300 million in 1973—a figure which the committee believes is justified because research into heart and lung diseases "should be expanded and accelerated in much the same way that the expansion and acceleration of the cancer programmes was initiated last year". And as for research into sickle cell anaemia, the committee has not altered the Administration's request for \$15 million for 1973, which itself represents a 15-fold increase since 1971.

But the biggest increase is slated to go to health manpower programmes. The committee suggests that these programmes should be funded \$738.6 million—an increase of \$205 million over the Administration's budget—and the bulk of the extra money is designed to go into the construction of new medical schools and nursing schools. The Administration's budget in fact contained no funds for construction, a situation which was defended on the grounds that sufficient money will be left over from this year's appropriations to fund all the planned projects. This argument did not convince the committee, however, which observed that the health manpower bills passed by Congress last year need to be matched with adequate funds if the present shortage of health manpower is somehow to be alleviated.

As for doctors, traineeships and fellowships administered by the National Institutes of Health, the committee notes that, for the fourth consecutive year, the Administration has planned for no increases, and recognizes that "this intolerably and dangerously static situation reflects an uneasy truce between the Office of Management and Budget, which would like to phase out these training programmes, and the Department of HEW". The funds requested for 1973 would in fact finance a total of 5,000 training grants and fellowships, compared with 7,650 in 1969. The

committee has therefore thrown its hand in with the Department of HEW by recommending that the programmes should be maintained at about their present level.

SPACE COMMITTEES

All Change at the Top

by our Washington Correspondent

MR GEORGE P. MILLER, Chairman of the House Committee on Science and Astronautics and in theory the most powerful member of Congress on scientific affairs, was defeated in a primary election in California recently. That means he will not be defending in the November elections the seat he has held since 1944 and a new chairman of the committee will be appointed next year. Miller, who is 81 years old, has served on the Committee on Science and Astronautics since it was first set up in the post-Sputnik panic that swept through US science policy.

In line for the committee chairmanship is Mr Olin E. Teague of Texas (assuming that the Democrats retain control of the Congress after the elections), who is the next longest serving Democrat on the committee. But he is already chairman of the Committee on Veterans' Affairs and will have to choose between the two; he is believed at present to be considering resigning his chairmanship of the veterans' committee to take on the Committee on Science and Astronautics. Mr Teague is also a founder member of the committee, and is chairman of the subcommittee on manned space flight. If he does not take on the chairmanship, it will then fall to Mr Ken Hechler, the next ranking Democrat in the longevity stakes, and a representative from West Virginia.

Mr Miller's departure from Congress also means that there will be a change in the chairmanship of both space committees, for Senator Clinton P. Anderson of New Mexico, chairman of the Senate Committee on Aeronautical and Space Sciences, is not seeking re-election. Anderson, who is 76, is likely to be succeeded by Senator Stuart Symington of Missouri, the next ranking Democrat on the committee who does not already hold a major committee chairmanship. If the Republicans gain control of the Senate, the chairmanship would probably go to Senator Carl T. Curtis of Nebraska.

NEWS AND VIEWS

Age Determinations and Lunar Evolution

AN important aspect of the lunar sample analysis programme during the past three years has been the attempt to piece together the history of the evolution of the Moon's crust and interior. A significant source of information about the early stages of this evolution is provided by radiometric age determinations and related isotopic information. For example, the limited time during which igneous rocks were produced on the Moon restricts the thermal evolution of the interior and the distribution of radioactive heat sources (principally U and Th). Current views have been modified by the Apollo 15 measurements of lunar heat flow—which is related to the total radioactivity of the Moon—and by the magnetometer measurements carried out by NASA's Ames Laboratory of the present temperature of the Moon's interior ($\sim 1,200^\circ\text{C}$).

The most informative of the radiometric age determination methods in use at present is that based on the decay of ^{87}Rb to ^{87}Sr . Rb-Sr data are frequently presented in the form of the so-called Sr-evolution diagram in which the ratio $^{87}\text{Sr}/^{86}\text{Sr}$ is plotted against $^{87}\text{Rb}/^{86}\text{Sr}$. (^{86}Sr is stable and acts as a reference isotope.) The rationale behind the use of this diagram for dating geological events (for example, the crystallization of a rock, or the large scale chemical differentiation of a whole region) is that at the time of the event to be dated the isotopic composition of Sr is assumed to be homogenized throughout the system under consideration (for example, on a small scale within the minerals making up an individual rock, or alternatively on a large scale within a whole suite of genetically related rocks). The chemical composition, and in particular the Rb/Sr ratio, is in general not homogeneous and on the Sr-evolution diagram the points would lie on a horizontal line. With the decay of ^{87}Rb into ^{87}Sr the points remain collinear but lie on a line (the isochron) the slope of which increases with the passage of time. The slope of the isochron indicates the time of the last Sr homogenization and the intercept indicates the original Sr composition. Both pieces of information are important in deducing not only the history of the individual rocks analysed but also the larger scale implications for the source material and from this for the planet as a whole.

Rb-Sr analyses and their interpretation by Wasserburg and Papanastassiou at the California Institute of Technology have played a major part in elucidating the story of the early development of the Moon. Isochrons obtained from suites of minerals separated from basalts from the lunar maria indicated that the Sr isotopic composition was homogeneous within individual rocks at times in the range 3.15×10^9 yr (Ocean of Storms) to 3.71×10^9 yr (Sea of Tranquility). These times are interpreted as representing the times of crystallization of the basalts from a liquid melt.

A unique rock from the Ocean of Storms with a granitic composition produced the oldest "mineral isochron" age so far from the Moon, 4.00×10^9 yr. Two such isochrons were obtained on groups of minerals separated from distinct fragments of the rock. Analyses of individual fragments (that is, without separation into the individual minerals) yielded a "whole rock" isochron age of $4.6 \times$

10^9 yr. The interpretation of this pattern briefly was that homogenization of the Sr isotopic composition in this rock last occurred 4.00×10^9 yr ago on a millimetre scale (that is, between adjacent minerals) as a result of a local heating episode but that on a centimetre scale the rock preserved (through inhomogeneities in Sr isotopic composition) a record of its existence, or the existence of its major components, from 4.60×10^9 yr ago. Measurements of argon retention ages by the ^{40}Ar - ^{39}Ar method at the University of Sheffield, and more recently at a number of other laboratories, are in good agreement with the Rb-Sr mineral ages, with the exception of one group of low K rocks collected by Apollo 11.

The chief inference which was drawn from these measurements of old ages from the maria—which on the basis of crater counts are known to be the youngest areas on the Moon—was that the radioactive heat sources within the Moon were at a very early stage concentrated within the outer 100 km or so of crust, thus providing a suitably short time constant for the conduction of heat to the surface. A similar conclusion follows from the more recent heat flow measurements. The high heat flow observed implies a high temperature gradient within the outer parts of the Moon but the magnetometer measurements indicated a relatively low central temperature. These observations can be reconciled simply by assuming that the heat sources are concentrated in the upper 100 km or so (an alternative explanation in terms of a high effective central conductivity, as by convection, is also possible but the chemical evidence seems to favour the concentration of U towards the surface).

Information concerning the Moon's history before 4.00×10^9 yr is less well defined but is provided by Rb-Sr systematics, in particular from a consideration of the "initial Sr composition" (intercept on the Sr-evolution diagram) and also the positions of the "whole rock" Rb-Sr compositions on the Sr-evolution diagram. Several conclusions have emerged. The initial Sr in several mare basalts was from the earliest measurements seen to be very primitive—close to the most primitive observed in achondritic meteorites—and implies that the source region of the basalts was greatly depleted in the radioactive parent Rb relative to Sr as compared with the solar abundance ratio. Also it implies that this depletion occurred at around the same time that the meteorites, and by inference the solar system, were formed. The depletion may have been associated with the original formation of the Moon.

A second feature concerns the Rb-Sr composition of the lunar soil and also the "whole rock" Rb-Sr compositions of the basalts. Plotted on an Sr-evolution diagram, these both define an approximate linear array with a mean slope corresponding to around 4.6×10^9 yr, the age of the solar system. At the time of Apollo 11 much was made of the apparent paradox of the soil being older than the rocks from which it is made. The paradox was more apparent than real because it arose from a failure by some commentators to understand the significance of the Sr-evolution diagram. The only real paradox at the time was the observation that the soil could not be con-

structed by grinding up the rocks at the site. This feature was recognized by the CalTech group who proposed an additional "magic component" rich in Rb which had been added to the fine soil (as a result of transport mechanisms which favour smaller fragments). The "whole rock" and soil 4.6×10^9 yr "isochron" are taken to reflect a large scale chemical differentiation (including Rb and Sr) and associated Sr-homogenization within the Moon at an early time, such as might occur with the formation of crustal regions with distinct chemical compositions.

The detailed explanations of the 4.6×10^9 yr isochron are not unique. The two simplest explanations assume that either (a) when the basalts formed, by the melting of some source region within the Moon, there was no appreciable chemical separation or differentiation of parent Rb from daughter Sr within the rock unit as a whole—thus the record of the early large scale chemical differentiation is preserved in the overall individual rock compositions; or (b) molten material from the interior produced in an Rb depleted region is intimately mixed with ancient crustal material rich in Rb. In this second explanation the 4.6×10^9 yr isochron is basically an isotope mixing line.

The CalTech group, while recognizing clearly the other possibilities, favour the second mechanism and point to a correlation of the initial Sr ratio in the basalts with Rb content. This correlation would follow naturally from a crustal contamination model. In model (a) the correlation implies a large number of chemically distinct source regions.

On page 446 of this issue of *Nature* O'Nions and Pankhurst, from the University of Oxford, draw attention to aspects of the CalTech Apollo 14 data which they feel are more naturally explained by model (a), or some variant, than by the contamination model. The CalTech measurements on separated minerals indicated isochron ages of 3.88 and 3.95×10^9 yr for these rocks. O'Nions and Pankhurst point out that the whole rock measurements define a rather convincing 4.31×10^9 yr isochron. (The CalTech workers presented the same experimental fact in an equivalent form in terms of model ages, in which an age is calculated for each measurement relative to primitive achondrite strontium.) Apollo 14 rocks are from the Fra Mauro formation which is generally regarded as ejecta from the formation of the Mare Imbrium basin, an important lunar feature. O'Nions and Pankhurst interpret the whole rock isochron as indicating an original crystallization of the material in the site of Mare Imbrium before its excavation and the younger ages are seen in terms of a reheating episode caused in part by the explosive excavation of the Imbrium basin.

By any standards the 4.31×10^9 yr isochron is impressive, though arguments can be raised which weaken the case for its interpretation in terms of a real event. There is a point of logic which implies that the fit cannot be perfect. Specifically the bottom two points of figure 1 in O'Nions and Pankhurst's communication lie on the same 3.9×10^9 yr mineral isochron and cannot therefore also lie perfectly on the same 4.3×10^9 yr whole rock isochron. This same argument applies to the upper three solid points where again the fit to the 4.3×10^9 yr isochron is not perfect. The slight difference in slope between 3.9 and 4.3×10^9 yr obscures the imperfection of the fit to the whole rock isochron. The effect of these arguments is to reduce the number of independent points on which the isochron is based. It could also be argued that the

breccia 14321 is a mixture and therefore simply defines a mixing line between igneous rock end-members. Taking the most jaundiced view it could be argued that the isochron is based on only four independent points (14053 group, 14276, 14310 group, and 14001, 7, 1) rather than on the eleven presented.

The Oxford letter will undoubtedly provoke further discussion of the lunar chronology. There is a natural tendency for lunar science to be an exercise performed exclusively by a group of investigators with access to samples. The extension of the discussion to the wider scientific community is a healthy sign.—From a Correspondent.

Dividing the Promoter

WHEN Jacob and Monod proposed their theory of the operon in 1961, they suggested that a small segment of DNA, called the operator, located at one end of a series of genes, might control their function. This would be the site, they suggested, where RNA polymerase might start transcribing the genes of the operon into a polygenic messenger RNA and where the repressor protein which controls the structural genes might act to stop transcription.

Later, more mutants of the lactose operon of *Escherichia coli* were identified to divide this region into two parts; the operator at which repressor protein binds and the promoter at which RNA polymerase apparently binds and starts transcription. A third site has recently been added, for the promoter itself may comprise an RNA polymerase binding site and a region where the cyclic AMP system acts to switch on inducible operons. All these sites are adjacent, however, in an order which suggests a simple model for the control of gene expression in bacteria: the repressor protein binds to a site between the genes and the promoter, in this way stopping RNA polymerase from proceeding into the genes. The most important revision of this model since the promoter was found is now reported in two articles in this week's *Nature New Biology* by Blattner and Dahlberg (237, 227, 1972) and Blattner *et al.* (*ibid.*, 232).

By using phage λ DNA as a template for RNA polymerase *in vitro*, Blattner and Dahlberg have found that four classes of RNA molecule may be made. During an incubation time of 0.4 minutes, each of these chains grows to about 175 nucleotides in length. By testing the ability of these molecules to hybridize with the single stranded DNA derived from a series of λ phages carrying deletions of genetically defined extent, the site from which each RNA is transcribed can be located. Phage λ contains two control sites, each consisting of an operator and a promoter, at which transcription of the phage starts during its active infection of a bacterium. Repressor protein can bind to each of these operators to block the activity of RNA polymerase from the adjacent promoter sites. More than 85 per cent of the RNA made *in vitro* originates from these two promoters. A small amount of RNA synthesis also occurs from two other regions, one of which seems to be a promoter site which is normally used later during the development of the phage; the other is a site not previously thought to act *in vivo* and whose significance is therefore obscure.

One of the two principal promoters is located on the "left" strand of phage λ DNA and the other on the "right" strand. The RNA molecules which correspond to these promoters can be hybridized to the appropriate single strands of DNA. Blattner and Dahlberg were able to measure the exact extent of hybridization by forming a hybrid of RNA with DNA, and then digesting any RNA which had not annealed with ribonuclease. The RNA bound to the DNA was then eluted and its sequence found from its fingerprints. The three RNAs corresponding to the three promoters identified *in vivo* all start with pppA; the other molecule begins with pppG. Only one of the three "A-starters" begins with an AUG sequence which could direct protein synthesis.

Does RNA synthesis start at the promoter site itself or elsewhere on the DNA? By using a series of deletion strains that all end to the left of the promoter on the left strand of λ DNA (which means that they cut to varying extents into the region from which the RNA molecule is made), Blattner and Dahlberg have pinned down the site on λ DNA at which the RNA can hybridize. Their technique is to see which oligonucleotide fractions are recovered from the RNA bound to the single stranded DNA isolated from these deletion phages. Their results show that the RNA corresponds to a stretch of DNA starting within twenty nucleotides to the left of the boundary between phages λ and 434 in the hybrid phage λ imm⁴³⁴, which contains the immunity region of phage 434 in place of λ 's own genetic material.

The promoter site itself has been defined by mutations which cause a reduction in the extent of synthesis of RNA; these are thought to act by reducing the affinity of the binding site on the DNA for the RNA polymerase enzyme. These experiments give a genetic map distance, in recombination units, of the promoter from the λ -434 boundary in λ imm⁴³⁴. Even though the distance of the RNA molecule from the point is measured in base pairs and that of the promoter in genetic map units, these results alone show that the two sites lie on opposite sides of the boundary. To measure the distance involved demands a calibration for map units in terms of base pairs. To achieve this conversion, Blattner *et al.* have turned to heteroduplex mapping, in which the DNAs of two phages are separated into single strands which are allowed to anneal with each other. Whereas regions of homology form a DNA duplex, substitutions or deletions show in the electron microscope as loops from the axis of the duplex DNA. The distance between the ends of the two deletions was measured in base pairs in this way and also in recombination units by genetic mapping, giving a conversion factor which should apply—perhaps not precisely, but within acceptable error—for the region involving the promoter and the site where RNA synthesis starts. Unfortunately, Blattner *et al.* have not published all the details of the mapping.

But these experiments show that the distance between the mutation which identifies the promoter and the boundary between λ and 434 in λ imm⁴³⁴ must be some two hundred nucleotides to the right. Even allowing for inaccuracy in these measurements (which are likely to be an underestimate rather than an overestimate), the distance between these two points is clearly very much larger than the diameter of RNA polymerase. As the point where RNA synthesis starts is within twenty nucleotides to the left of the boundary, this means that RNA polymerase must bind to DNA at the promoter, but starts transcrip-

tion at a point some 200 nucleotides to its left. One essential question to answer is whether the RNA molecules synthesized *in vitro* start at the same point as those made in an infected bacterial cell. Blattner and Dahlberg say that they have evidence that this is indeed so.

How can the gap between the binding site and the startpoint be explained? Blattner *et al.* suggest two models. One possibility is that the DNA takes up some tertiary conformation so that the two points are close together; this might be aided by some protein which would then, *de facto*, be a positive regulator protein whose role would be to enable RNA polymerase to move from binding point to startpoint. But the drawback of this model is that it all but creates a second binding point, for RNA polymerase would have to leave one part of the DNA in order to attach to the other. On teleological grounds therefore this model seems less likely than the alternative which Blattner *et al.* suggest, which is that RNA polymerase "drifts" from the binding point to the startpoint, without synthesizing RNA.

This model has the attraction that the drift region between the promoter and startpoint could include various regulator sites at which repressors would bind to help create barriers to drift which would prevent expression of the adjacent genes. Alternatively, positive regulator proteins might help to overcome natural barriers to drift. The model implies that the operator, if it lies between binding point and startpoint, could act without itself being transcribed into RNA. One particularly important project for future research will be to determine where the operator mutants map in relation to these two sites. Indeed, in a note added in proof, Blattner and Dahlberg say that the sequences of the RNAs made by two operator mutants are identical to those found previously. This shows that, whatever the precise location of the operator, it is not transcribed into RNA. Yet another prediction of the model is that several RNA polymerase molecules might be able to queue up in the drift region, without starting transcription; this would explain why more RNA polymerase molecules seem to bind to λ DNA than RNA chains are started.

Does this model apply to other systems, such as bacterial operons? Unfortunately, only genetic mapping is available for these operons and mutants in the promoter binding region and startpoint would presumably have the same characteristic: the adjacent genes cannot function. Whether this happens because RNA polymerase cannot bind at one site or cannot initiate synthesis at the other would not be apparent from the behaviour of the mutants. Indeed, it is possible that some of the "promoter" mutants already identified in, for example, the lactose operon might be located in a startpoint rather than a binding region. Although there is no evidence to support or deny this idea, it is appealing to suppose that the same sort of structure is used to regulate both bacteriophages and bacterial operons.

The implication of the conclusion that two separate sites are involved in binding RNA polymerase and starting transcription, in phage λ at least, is that the region identified by "promoter" mutations may contain the operator site(s) within it and thus have precisely those characteristics originally attributed to the operator by Jacob and Monod in 1961: to bind RNA polymerase, initiate transcription, and control the expression of the adjacent genes. Now, however, by an irony of etymology, this nomenclature has been reversed.—B. L.

How *Lac* Repressor binds to *Lac* DNA

THE experiments published in *Nature* two weeks ago (*Nature*, **237**, 323; 1972) by Müller-Hill and his several colleagues, which have led to a structural model of how *lac* repressor protein binds specifically to the operator region of the *lac* operon, provide a remarkable example of the sophistication that is nowadays the hallmark of the molecular geneticist.

Ever since Gilbert and Müller-Hill first isolated *lac* repressor protein in 1967, evidence has been steadily accumulated, all of which indicates that the *lac* repressor protein prevents the coordinated expression of the three structural genes of the *lac* operon by binding to a specific region of the operon called the operator. And it is envisaged that in so doing the repressor blocks DNA dependent RNA polymerase from binding to the operon and transcribing it into a single messenger RNA molecule containing the information to specify the three enzymes of the operon. Furthermore, investigations of pure repressor protein, which of course can also bind inducers of the operon and as a result suffer an allosteric change which prevents its binding to the operator, have revealed that, with a molecular weight of about 160,000, it is made of four identical polypeptide subunits and that it does not contain nucleic acid.

All these observations provide more than a superficial description of the natural history of the *lac* repressor but they do not satisfy anybody curious about the structure of the repressor, the topography of its interaction with the operator and the basis of the specificity of this interaction.

From the many precedents provided by enzymologists who have shown that the active sites of enzymes are usually located in clefts in enzyme molecules into which substrate molecules can fit, it seemed reasonable to anticipate that the *lac* operator DNA would be found to fit in a cleft in the repressor molecule. The data belie any such expectations, however, for Müller-Hill and his associates believe on the contrary that protrusions from the repressor molecule, comprising the first (5') fifty amino-acids of each subunit, specifically bind to the operator region.

Genetic data provided the first clue that the 5' terminal regions of the

repressor subunits are involved in the specific binding to DNA. Mutants of the *lac* repressor which have lost the ability to bind to the operator but can still bind inducer molecules all map at the 5' end of the repressor gene which specifies the first fifty amino-acids of the repressor protein. Moreover, genetic analyses indicate that the operator and inducer binding sites are not very closely connected.

Analysis of the first fifty amino-acids at the 5' terminus of the repressor subunit chain revealed only one unusual feature, this short region of the molecule contains half the total tyrosine residues, but the sequence is otherwise unremarkable. Some 247 point mutations, however, which result in the change of one or another of these fifty amino-acids all also result in a repressor which cannot bind to the operator DNA. This region of the molecule is most probably therefore directly involved in this binding. A sequence of fifty amino-acids is, however, scarce enough to form a cleft, but it could form a protrusion from the repressor molecule and if the protruding stretch assumed an alpha helical configuration it could fit into the deeper of the two grooves of B form double helical DNA.

By playing, as they put it, with

space filling molecular models, the Cologne group found that only one part of the 5' terminal region of a repressor subunit—that between amino-acids 17 and 33—can fit into the deeper groove of double stranded DNA and simultaneously bind both to phosphates of the DNA backbone and the polar groups of the bases in the groove in such a way that the four possible base pairs can be distinguished from each other. This segment of the repressor subunit, they argue, is therefore critical for binding to the operator DNA. But that is not all; from the space filling models Müller-Hill and his colleagues have predicted the sequence of eight base pairs which are recognized by the protruding 5' end of a repressor subunit and they believe this sequence may, in the operator region, be repeated four times, with intervening spacers, so that each subunit of the repressor can recognize the same DNA sequence.

Of course it would be surprising indeed if in every detail this model proves to be correct, but at the very least it should greatly stimulate attempts to sequence the operator DNA and once that sequence is known the validity or otherwise of the model will be immediately apparent. —From a Correspondent.

Feline Leukaemia Virus sensitive to Interferon

IN next Wednesday's *Nature New Biology* (June 28) Merigan, Rodgers, Hardy, Old and Kassel add feline leukaemia virus (FeLV) to the list of RNA tumour viruses that have been shown to be sensitive to interferon. Merigan and his colleagues prepared feline interferon from the feline kidney cell line CrFK which they had infected with Newcastle disease virus. They then assayed the ability of this interferon to block the infection of CrFK cells and cells of the feline fibroblast line, FFc60wf, by FeLV. The virus was prepared by membrane filtration of supernatant fluid from cultures of cat cells chronically infected with FeLV, and infection of the CrFK and FFc60wf cells was assayed by an indirect immunofluorescent antibody test which detects in cells the FeLV group-specific antigen.

By treating cells with the interferon 24 hours before their infection with FeLV, Merigan *et al.* caused a significant decrease in the number of infected cells. As in other systems the dose

response curve of the interferon proved to be sigmoidal and the maximum inhibition of infection was some 80 per cent, which, as Merigan *et al.* comment, may mean that a minority of FeLV may be resistant to the action of interferon.

The results of a range of tests, including parallel assays of the anti-vesicular stomatitis virus activity of the interferon and of the effects of varying the time and duration of exposure of the cells to interferon, indicate conclusively that it is the interferon itself and not some contaminant of the interferon preparations which is aborting the FeLV infection. Moreover, exposure of the cat cells to interferon alone proved that, at least at the concentrations used, it is not cytotoxic.

Like Rous sarcoma virus and murine sarcoma and leukaemia viruses, feline leukaemia virus is apparently sensitive to interferon *in vitro*, and now Merigan *et al.* are investigating the effects of interferon on cats with virus associated leukaemia.

SPECTRA

All Done by Resonance

from our Molecular Biology Correspondent
YET another spectroscopic technique has, it seems, been cast up on the wilder shores of biochemistry. This is a variant, long familiar to spectroscopists, of the Raman effect, the possibilities of which have been greatly widened since the introduction of laser sources. Lest all readers forthwith lower their lorgnettes and look for less rarefied topics on which to exercise their minds, it should be added that the technique, where it is applicable, is devoid of the two great drawbacks of Raman, and for that matter, infrared spectroscopy as applied to biological systems; namely, the complexity of the spectra, and the distressingly large concentrations of the solutions that are needed.

The method makes use of a resonance phenomenon, whereby anomalously large scattering is produced when the wavelength of the incident light falls within an electronic absorption band of the molecule. The intensity is such that spectra can be observed under these circumstances from species present at concentrations several orders of magnitude lower than otherwise necessary. With a choice of rare gas lasers available, there is a good chance of finding a wavelength that fulfills the resonance condition for coloured molecules.

One of the most attractive prospects for this technique is the possibility that it may be used to isolate the Raman spectrum of a ligand binding to a macromolecule, such as a protein, from which something of the nature of the binding and the state of the bound species might then be divined. The first report of an exploration of such a system comes from the stronghold of molecular spectroscopy in Ottawa, and concerns the interaction of methyl orange with bovine serum albumin. Carey, Schneider and Bernstein (*Biochem. Biophys. Res. Commun.*, **47**, 588; 1972) have used an argon laser to excite within the visible absorption band of the dye in aqueous solution at a concentration of only 10^{-5} molar. A series of lines in the Raman spectrum has been assigned in terms of the structure, including azo-group modes, and a phenyl-nitrogen and a C-N stretch. In the solid state, the bands are shifted to shorter frequencies, and the spectrum comes closely to resemble that of the dye in solution in the presence of a large molar excess of albumin.

From this emerges the first conclusion, that in its bound state the dye is in a non-aqueous environment, and therefore presumably seated in a crevasse in the protein. The angular relation of the phenyl groups is evidently unchanged on binding, for any twist about the azo bond (such as has

been suggested to occur) would be strongly manifested in shifts of a sensitive frequency. Indeed no anomaly is observed in any of the frequencies involving azo or amino nitrogens, apart from the small environmental effect. The dye also contains a sulphonate acid group, one frequency having been identified as relating to its state, and from a comparison with arsonate analogues, it is deduced that water molecules or ions in its vicinity are asymmetrically disposed. Carey *et al.* note that an analysis of intensities of aromatic ring frequencies might allow one to infer interactions with aromatic side chains in the protein.

Now whereas these findings are not in themselves such as to send protein chemists into any paroxysms of excitement, they plainly point the way the resonance Raman technique might very usefully develop. There are many protein-ligand systems of greater biological cogency to which it might be applied, some indeed where it is known, or thought, that the ligand binds in a configurational state different from that in free solution, or where it is involved in multiple interactions with subsites on the protein. Another possible application has been perceived by Strekas and Spiro (*Biochim. Biophys. Acta*, **263**, 830; 1972), who have used an argon-krypton laser, emitting at 5682 Å, to excite resonance Raman spectra of the prosthetic group in haemoglobin in various states. The spectra of deoxy-, oxy- and carboxyhaemoglobins and

methaemoglobin (ferric) derivatives are largely similar, though there are considerable differences in intensity.

Two bands in particular, however, seem to reflect the state of the iron, for they are present in both oxy- and carboxyhaemoglobin, but are missing in deoxyhaemoglobin. In methaemoglobin azide they are again prominent, but in the acid form of methaemoglobin, where the sixth iron ligand is water, they are weak. The distinguishing feature between these forms is that the iron atom lies in the plane of the haem ring in low-spin derivatives, but appreciably out of plane in those of high spin. The last include deoxyhaemoglobin, where the crystallographic analyses of Perutz show the iron to protrude 0.8 Å above the plane, and acid methaemoglobin, where it is 0.3 Å out of plane: Strekas and Spiro have found that the sensitive bands serve as a marker for the acid-base titration of the methaemoglobin.

The frequencies in question are thought to arise from carbon-carbon double bonds in the haem, which respond to the movement of the iron, by way of a pucker induced in the ring system. The bands might well be put to the same kind of use as structural indicators as the hyperfine-shifted resonances in the NMR spectra of haem proteins. It is somewhat disappointing that no frequencies arising from the iron-bound ligands are to be seen: evidently the resonance conditions in these cases are not fulfilled.

Phytochrome Intermediates *in vivo*

THE plant photomorphogenic pigment phytochrome is responsible for developmental processes initiated by brief treatments with low irradiances of red light, or by continuous irradiation with high energies of broad spectrum light (the so-called high energy reaction). Attempts to account for this reaction have centred principally on the fact that the two photoconvertible forms of phytochrome (P_R and P_{FR}) have overlapping absorption spectra and thus under continuous irradiation a photo-stationary state is established with characteristic proportions of the two forms depending on the wavelengths.

Most workers have assumed that P_{FR} is the active form of phytochrome and that treatments which maintain P_{FR} for long periods of time will have maximum morphogenic effect. It is known from flash spectroscopic studies that several intermediates are formed during the photoconversions of P_R and P_{FR} , some of which have a relatively long half-life (Linschitz *et al.*, *J. Biol. Chem.*, **241**, 3395; 1966). Although the existence of these intermediates *in vivo* was shown by Briggs and Fork in 1969 (*Plant Physiol.*, **44**, 1081), inadequate

instrumentation has up till now prevented the estimation of how much of the total phytochrome exists as intermediates during continuous irradiation. In its turn this has prevented the determination of $P_{FR}:P_{total}$ proportions.

Fortunately, C. J. P. Spruit, of Wageningen, who designed the instrument which first proved the presence of P_{FR} in dark-imbibed seeds (Boisard *et al.*, *Meded. LandbHoogesch. Wageningen*, 68-17; 1968) has successfully developed an *in vivo* spectrophotometer equal to this new task, and in next Wednesday's *Nature New Biology* (June 28) Spruit and R. Kendrick report some results achieved with this instrument.

Spruit and Kendrick clearly demonstrate for several tissues that under continuous incandescent white light, up to 30 per cent and more of the total phytochrome is present as conversion intermediates. Furthermore, the proportion in the intermediate forms varies with light intensity. The high levels of intermediates will come as a shock to many workers in this field and are clearly of importance to an understanding of phytochrome action in the high energy reaction.

STEROID RECEPTORS

Allosteric Proteins?

from a Correspondent

BINDING of a steroid to specific cytoplasmic receptor proteins is thought to be the first critical step in the pathway leading to modification of gene expression in target tissues. According to all current hypotheses the steroid-receptor complexes migrate from the cytoplasm into the nucleus, but controversy exists as to whether they then bind to DNA, to non-histone proteins, or to both, or deliver the steroid to other receptor proteins. It is also argued that the receptor proteins have an additional regulatory role in the cytoplasm.

Whichever particular hypothesis is favoured, investigation of the nature and properties of the cytoplasmic receptor proteins is undoubtedly of high priority, not only for understanding how steroids work but also for clues as to how other cytoplasmic proteins may influence gene expression. Unfortunately, attempts to isolate and purify steroid receptors on a large scale have so far not met with much success, so partially purified or crude cytoplasmic extracts have been used. Nevertheless, even this approach has enabled some interesting predictions about steroid receptor behaviour to be made, the latest of which is to be found in an article in the *Journal of Molecular Biology* by Rousseau, Baxter and Tomkins (67, 99; 1972), who have used as a model system the induction by glucocorticoids of tyrosine aminotransferase (TAT) in hepatoma tissue culture cells.

Earlier experiments using whole cells had shown that steroids could be divided into four classes on the basis of their ability to influence TAT induction, "optimal" inducers such as corticosterone and dexamethasone stimulated a large (up to ten-fold) increase in TAT activity, whereas "sub-optimal" inducers (such as 11- β -OH-progesterone) produced only a small induction of TAT even at high concentrations, and reduced the level of induction achieved by a given amount of dexamethasone. "Anti-inducers" such as progesterone and 17- α -methyl-testosterone also inhibited induction by dexamethasone but were themselves unable to induce significant amounts of TAT. Finally, "inactive" steroids neither produced nor inhibited TAT induction.

These observations led to the proposal (Samuels and Tomkins, *ibid.*, 52, 57; 1970) that the glucocorticoid receptor is an allosteric protein existing as an equilibrium mixture of two conformational states, only one of which is active in eliciting TAT induction. According to this model, optimal inducers bind to the active form of the receptor and shift the equilibrium in its favour, whereas anti-inducers bind to the inactive form

and reduce the availability of active receptor. Sub-optimal inducers can bind to both forms of the protein, whereas inactive steroids do not bind at all.

Rousseau *et al.* have now taken these experiments a step further and, using a simple and rapid assay, have looked at the ability of different steroids to bind *in vitro* to cytoplasmic extracts of hepatoma cells. They have found that optimal inducers bind to a single class of receptor sites with an affinity proportional to their potency in inducing TAT in whole cells. The anti-inducer progesterone also binds to a single class of receptor sites and competitively inhibits dexamethasone binding. Assuming that the receptors for progesterone and dexamethasone are the same (and the number of binding sites calculated for both steroids is very close), the extent to which the anti-inducer competes is predictable from the relative affinities of the two steroids for their binding sites, and accounts nicely for the ability of progesterone to inhibit TAT induction by dexamethasone in whole cells. Thus the behaviour of the different steroids in cytoplasmic extracts closely parallels their biological activity and is still compatible with the model predicted by Samuels and Tomkins. Rousseau *et al.* go on to describe experiments designed specifically to test this model.

It had been noted previously that un-

complexed receptors (presumably in the inactive form) were more thermolabile (and also more tightly bound to glass and other surfaces) than those complexed with dexamethasone. It was argued that if progesterone bound to the inactive form of the receptor, the progesterone-receptor complex should be more thermolabile than the dexamethasone or cortisol-bound (active) receptor, and this is indeed what is observed. In addition the different kinetics of the association of dexamethasone, cortisol and progesterone with the receptor are consistent with a conformational change taking place after binding of the inducers, but not the anti-inducer. Another piece of evidence in favour of the allosteric model is the observation that, unlike the dexamethasone-bound form of the receptor, the progesterone-bound molecules do not accumulate in the cell nucleus.

By modifying different groups on the progesterone and corticosterone molecules, Rousseau *et al.* were able to establish which parts of the steroid structure determine the affinity of the compound for the active or inactive conformations of the receptor. This sort of approach could obviously be very useful in the design of new steroid drugs, but it remains to be seen whether natural anti-inducers play any part in modulating the activity of glucocorticoids *in vivo*.

Model for Type I Supernovae

MANY explanations have been put forward to account for Type I supernovae, but none has yet proved entirely satisfactory. The latest step in the slow progress towards an understanding of these violent eruptions comes from F. D. A. Hartwick, who suggests (in next Monday's *Nature Physical Science*, June 26) that explosive hydrogen burning caused by mass transfer in a binary system could be the driving force.

The particular difficulty in constructing models of Type I supernovae is that they occur chiefly in elliptical galaxies which are thought to contain stars with masses $\lesssim 1 M_{\odot}$. It is not too difficult to explain how a very massive star might explode as a result of a sudden collapse after one stage in the nuclear burning process has been exhausted. In that case, collapse and consequent heating of the stellar interior can occur until the next fusion reaction begins, and this can certainly take place explosively. But a low mass star should, in theory, sit quietly, burning its nuclear fuel as far as possible and then cooling into a white dwarf.

In contrast to this naive picture, Hartwick's models produce violent Type I supernovae in systems where one component is very low mass indeed—about $0.1 M_{\odot}$. The key to the process is that

such a star will evolve over a time scale of $\sim 1.23 \times 10^9$ yr until the central temperature is falling and the centre of the star is becoming degenerate while unburnt hydrogen remains in the outer layers—just the picture of a quiet white dwarfish old age outlined earlier. But because Hartwick's models are members of binary systems they are not left in peace to enjoy a respectable retirement. If the companion to such a $0.1 M_{\odot}$ star is itself about 0.7 to $1.0 M_{\odot}$, by the time its small companion is settling down the larger star will be expanding, during the normal course of evolution, and transferring mass to its small, degenerate partner. This is literally an explosive situation. A cooling, but still hot, degenerate star is being compressed by the sudden addition of mass from outside.

According to Hartwick, this could raise its internal temperature abruptly, suddenly igniting another round of nuclear burning throughout the remaining hydrogen, and resulting in a violent explosion; this can occur for only a moderate amount of mass transfer, because of the low initial mass of the smaller partner in the binary pair. More detailed calculations are clearly needed, but as it stands this model is as good as most of the other explanations of Type I supernovae proposed so far.

TISSUE GROWTH

Chalones after 15 Years

from a Correspondent

TISSUE specific proliferation control in multicellular organisms is *sine qua non*, but the elucidation of such control mechanisms depends on a combination of satisfactory assay methods and analytical biochemical techniques of sufficient resolution. The concept of a negative feedback system was elaborated some 15 years ago by Weiss and Kavanau, and Bullough, who demonstrated mitotic inhibition in the epidermis by an epidermal extract, adopted the term "chalone" to denote such proliferation inhibiting feedback substances.

In the hope of clarifying both conceptual and methodological questions, the first international chalone conference was held at the Upjohn Company's Brook Lodge, Augusta, Michigan, on June 5-7, under the auspices of the National Cancer Institute and Office of Naval Research. The first day was devoted primarily to epidermal chalones, the second to the lymphocytic and granulocytic chalones and the third to miscellaneous (fibroblast, liver, lung, kidney, melanocyte) chalones. It was soon evident that although the chalone concept involves the physiological control of cell population sizes, the operational definitions vary (at present) from inhibition of the G_2 or G_1 or S phases of the cell cycle to inhibition of growth of cell lines and to depression of the cellular immune reaction.

Extracts from skin epidermis, for example, produce a G_2 inhibition as reported by Bullough, Lawrence, Iversen, and others. Dr E. Lawrence (University of London) explained that the previously reported potentiation of this effect by stress hormones does not seem to result from an interaction between chalone and, for example, adrenaline. These extracts contain, however, a G_1 inhibitor too, and Dr K. Elgjo (Rikshospitalet, Oslo) and Dr F. Marks (Deutsches Krebsforschungszentrum, Heidelberg) reported that this does not seem to be identical with the G_2 inhibitor. Although the molecular sizes are both in the range of 10,000-30,000, the G_1 inhibitor seems to be heat stable, insensitive to proteolytic enzymes and metabolically more stable than the G_2 inhibitor.

The biological assay of lymphoid tissue extracts (such as spleen and lymph nodes) is more satisfactory. Dr J. C. Houck (Children's Hospital, Washington), for example, reported a "chalone" concentrate which inhibits the onset of DNA synthesis in stimulated lymphocytes without, however, affecting their phenylalanine uptake. This means that it is not merely

cytotoxic. The concentrate also inhibits growth of lymphoid cell lines *in vitro*, without affecting fibroblast growth. The inhibition of the immune system by purified and concentrated extracts has been demonstrated by Drs E. Garcia-Giralt and M. Kiger (Hôpital Paul-Brousse, Villejuif) using the GVH, graft rejection and MLC reactions and the formation of 19S cells. The lack of cytotoxicity was shown by inhibition of ^3H -thymidine uptake by such preparations, without affecting RNA or protein precursor uptake.

The granulocytic "chalone", reported on by Dr T. Rytomäa (University of Helsinki) and Dr W. R. Paukovits (University of Vienna), is about one-tenth the size of its lymphocytic counterpart. This small polypeptide inhibits DNA synthesis in the bone marrow cells and has some marked inhibitory effects on experimental myeloid leukaemia in rats. Its biological specificity is, however, not yet as clearly established as, for example, that of the lymphocytic "chalone". Indeed, cell group specificity rather than precise cell population specificity cannot be excluded until further purification of the respective tissue extracts.

A specific fibroblast growth inhibiting factor of molecular weight about 30-50,000 with similar chemical properties to the lymphocytic chalone was

reported by Dr Houck, but this does not inhibit the PHA reaction. Apart from its broader aspects, the possibility of depressing fibroblast overgrowth in primary explants of epithelial tissue should make such a substance very attractive. A byproduct of this work was the finding of a serum factor which enables diploid fibroblast to grow in media which are otherwise serum free. Experimental evidence for a liver chalone was discussed by Dr M. P. Stack-Dunne (National Institute for Medical Research, London) and Professor W. G. Verly (University of Montreal). This inhibitory compound is unusual in that it is a very small molecule (about 1,000 daltons) and inhibits ^3H -thymidine and amino-acid uptake by liver slices but not, apparently, by kidney slices. Evidence for chalones was also reported in lung and kidney organ cultures by Dr. J. Simnett (Royal Victoria Infirmary, Newcastle) and Dr D. P. Chopra (Temple University, Philadelphia). The role of the flow rate of the blood in the regeneration of lungs was emphasized.

Apparently, even tumour cells do not escape some feedback control of growth—and again this may be specific. Dr P. Bichel (Cancer Research Institute, Aarhus) described a specific effect in a mixture of two different kinds of ascites tumour cells *in vivo*. The

Subunit Interactions in Haemoglobin

Two articles in next Wednesday's *Nature New Biology* (June 28) deal with structural and spectroscopic properties of an abnormal haemoglobin, and draw some inferences that relate to conformational equilibria in haemoglobin generally. The abnormal species is haemoglobin M Milwaukee-1, which has a mutation in the β -chain, leading to an abnormally high reduction potential, such that both β -chain haems are normally in the ferric state. The substitution occurs in the haem pocket, on the side normally occupied by ligands, and is of a glutamic acid for a valine.

The oxygenation properties of the normal α -chains are surprisingly different from those in the apparently comparable hybrid of normal ferrous α -chains and normal cyanmet- β -chains. Unlike the last species, the Milwaukee variant shows haem-haem interactions and a considerable Bohr effect. This is explained, as Perutz, Pulsinelli and Ranney now find, by the crystal structure, which is isomorphous with that of deoxyhaemoglobin, not, as in all other ferric species so far known, with oxyhaemoglobin. When the α -haems are oxygenated or oxidized, the structure becomes similar to normal met- (or oxy-) haemoglobin.

That this finding signifies a change

in the β -chain from the deoxy- to the oxy-type conformation is confirmed by a change in absorption bands of the ferric haem, when the α -chains are oxygenated, in wavelength regions known to reflect the spin state, and hence the conformation of the derivatives. Thus, as with the oxygenation reaction, the conformational change in the abnormal ferric β -chains is linked to the movement of the iron atom out of the plane of the haem. In the methaemoglobin subunits the out-of-plane displacement is small, indicating that the conformational equilibrium is less strongly biased towards the oxyhaemoglobin-type state, and the molecule can exist in either form.

In an accompanying article, Lindstrom, Ho and Pisciotto have examined the characteristic hyperfine shifts in the NMR spectrum that arise from the haem groups. The magnitudes of the shifts in the α -chain haem spectrum are identical with those in normal deoxyhaemoglobin. Six β -chain resonances are observed, and when the α -chain iron atoms are liganded with carbon monoxide, one of these peaks undergoes a considerable shift, indicating that events at the α -haem affect steric features in the ferric β -haem, as the results of Perutz *et al.* demand.

inhibitory substance in this case seems to be a large molecule, unlike the one which inhibits the growth of the Harding Passey melanoma *in vitro* (but not that of Chinese hamster fibroblasts). The molecular size of this last compound is less than 10,000 and is destroyed by trypsin or neuraminidase, and, according to Dr D. L. Dewey (Mount Vernon Hospital, Middlesex), it also causes a marked "maturation" of the melanoma cells *in vitro*.

The kinetics of the interlinked cell populations in haemopoietic tissue was discussed by Dr L. Lajtha (Holt Radium Institute, Manchester) who emphasized the techniques necessary for identification of specific chalone effects in this cell system. Finally, the possible mechanism of loss of specific tissue function control was discussed by Dr B. Rabin (University College, London) in an elegant demonstration of membrane changes produced by carcinogens, an illustration on how "chalone" control may be lost by the cells.

CANCER RESEARCH

Activating Carcinogens

from our Cell Biology Correspondent

ONE of the ironies of cancer research is that although chemical carcinogens, such as the polycyclic aromatic hydrocarbons, are chemically simpler structures than RNA or DNA tumour viruses, chemical carcinogenesis is less amenable to investigation than is viral carcinogenesis. Chemical carcinogenesis seems to be a hit and run affair, which does not depend on the persistence of the carcinogen once it has hit its target, whereas the maintenance of the transformation of cells infected with cancer viruses seems to depend on the continuous expression of viral "transforming" genes.

By exploiting strains of virus which carry conditional lethal mutations in the "transforming" genes and by identifying all the proteins specified by a tumour virus genome it should be possible to identify not only the transforming proteins but their cellular targets. The elucidation of the biochemistry of chemical carcinogens, by contrast, is a more formidable task. First, it must be determined whether a metabolite of any compound administered rather than the compound itself is the carcinogen and then its target must be identified. Added to which it is only comparatively recently that cultivated cells which reproducibly are susceptible to chemical carcinogenesis have become available.

Heidelberger and his colleagues, for example, have used cultivated mouse prostate cells with notable success to confirm Boyland's old suggestion that at least some polycyclic hydrocarbons are activated by being metabolized into K epoxides. Their latest report shows

that the K region epoxides of benzanthracene, dibenzanthracene and 3-methylcholanthrene are both more cytotoxic and more carcinogenic for mouse prostate cells than are the parental hydrocarbons (Marquardt *et al.*, *Cancer Res.*, **32**, 716; 1972). The K region epoxides of methylbenzanthracene and the bromomethyl substituent by contrast are less potent carcinogens than are the parental molecules.

In a subsequent report (*ibid.*, 721), Marquardt and Heidelberger describe experiments in which mouse prostate cells were cultivated with lethally irradiated feeder layers of either rat or mouse embryo cells while exposed to various polycyclic hydrocarbons. The idea behind these experiments was to test the effect on cytotoxicity and carcinogenicity of the hydrocarbons for prostate cells of feeder cells either more or less able to metabolize the hydrocarbons than the prostate cells.

As expected, the addition of feeder layers of cells which readily metabolize the hydrocarbons to K epoxides resulted in a significant increase in the cytotoxicity and carcinogenic potential of those hydrocarbons which need to be metabolized to an active epoxide. Feeder layers of human skin cells, which metabolize these compounds to a lesser extent than do the mouse prostate cells, also failed to alter the yield of transformed mouse cells. Moreover, the addition of drugs which either induce increased or decreased intracellular levels of mixed-function oxidase

activities had the expected effect on the yield of transformants obtained with given doses of methylcholanthrene and benzanthracene. These data therefore also support the hypothesis that at least some non-methylated, polycyclic, aromatic hydrocarbons have to be metabolized to K epoxides in order to be carcinogenic, and of course the feeder layer technique provides an assay for the extent to which cells from various sources can bring about this step.

Asbestos, like hydrocarbons, is a carcinogen and considerable effort has gone into trying to determine whether or not asbestos *per se* or some contaminant is responsible for neoplastic transformation. According to Starton and Wrench, who report the results of experiments with rats started more than 2 years ago (*J. Nat. Cancer Inst.*, **48**, 979; 1972), the carcinogenicity of asbestos may depend on its physical structure rather than its chemistry.

Starton and Wrench compared the carcinogenicity of crocidolite, amosite and chrysotile asbestos milled to various extents and administered on a fibreglass vehicle. They believe that under their conditions "the structural integrity of the asbestos fiber above that of the finest submicroscopic fibril is essential to carcinogenicity and that neither contaminants nor chemical components are likely factors". If this is the case it will be interesting to see if similarly sized fibres of other materials of comparable durability are carcinogenic.

Granulocyte and Macrophage Differentiation

ELUCIDATING the molecular basis of cell differentiation is currently one of the chief preoccupations of many biologists and of the several systems that have attracted attention perhaps the most amenable to further detailed investigation is the differentiation *in vitro* of haematopoietic stem cells into mature granulocytes and macrophages. Sachs and his colleagues are among the pioneers in this field and their latest contribution appears in *Nature New Biology* next week (June 28).

Sachs and his colleagues have previously shown that a protein factor with a molecular weight of between 65,000 and 70,000 which is released by cultivated mouse fibroblasts will, when supplemented with an adenine nucleotide cofactor, induce normal mouse stem cells to differentiate into granulocytes and macrophages. Sachs *et al.* have now investigated the ability of this factor to induce the differentiation *in vitro* of myeloid leukaemic stem cells from mice. Crude preparations of the inducing protein—serum-free medium conditioned by mouse fibroblasts—

increase some seven to eight-fold the cloning efficiency in soft agar of the myeloid stem cells; crude factor also causes about 5 per cent of the colonies to differentiate to granulocytes and 45 per cent to differentiate to macrophages.

By ultrafiltration Sachs *et al.* then separated the protein factor in the crude preparations from the low molecular weight nucleotide cofactor and assayed the ability of the protein inducer, in the absence of cofactor, to stimulate differentiation of normal and leukaemic stem cells. They found that whereas the induction of differentiation of normal stem cells depends on cofactor as well as inducer, colonies of myeloid leukaemic stem cells differentiate when exposed to the protein inducer alone, and addition of adenine nucleotides failed to increase the proportion of differentiated colonies.

It seems therefore that unlike normal stem cells myeloid leukaemic stem cells of mice produce the adenine cofactor required to potentiate the differentiation-inducing protein. At the very least this finding may form the basis of a diagnostic test for myeloid leukaemia blast cells.

Human Growth Hormone

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Human growth hormone is a successful treatment for children who without it would grow up to be midgets. This article describes present knowledge of its physiology, its role in the regulation of growth and its effect in treatment.

DURING the past ten years the availability of a preparation of human growth hormone has provided a wholly successful treatment for a class of dwarfed children who previously had to pass their lives as midgets. An example is given in Fig. 1. In addition it seems likely that current experimental work on the physiology of the hormone will elucidate for the first time the mechanism by which growth of children and young animals is regulated¹ and provide explanations for the diminution of growth velocity with age, and for the mechanism of catch-up growth after starvation or illness². The subject is thus topical for both medical and biological reasons.

Human growth hormone (HGH) is a protein of molecular weight 21,700 consisting of 190 amino-acids^{3,4}. Growth hormone from cattle, sheep and pigs is very similar though not identical in structure (Bellair *et al.* and Santome *et al.* in ref. 5) but all forms are sufficiently different from HGH not to be active in man. This contrasts with the situation for adrenocorticotrophic hormone (ACTH) where hormone derived from these sources is effective clinically.

There are two other hormones very similar in structure to HGH, and probably derived from the same parent molecule in evolution (Niall, ref. 5). These are placental lactogen (chorionic somatomammotropin) and prolactin (lactogenic hormone).

Human placental lactogen has 190 amino-acids, like HGH, and of these all except 28 (ref. 6) to 30 (ref. 3) correspond. Twenty-two of those that are different can be explained by only a single base change in the triplet codon. Placental lactogen is secreted into the maternal circulation by cells of the syncytiotrophoblast of the placenta, in amounts increasing gradually from early pregnancy to nearly 1 g/day shortly before term. It has most of the metabolic actions of growth hormone, and will cause some growth in children who are growth hormone deficient. However, it is only about one-hundredth as active as HGH in this respect (Grumbach *et al.*, ref. 5). Whether it acts directly on the foetus to cause it to grow *in utero* is doubtful. Anencephalic foetuses, however, which lack pituitary glands, are normal in size, and children who cannot secrete growth hormone nevertheless have a normal birth weight (though they may be slightly reduced in birth length). Maternal growth hormone does not cross the placenta⁹.

Prolactin is synthesized and secreted by the human pituitary gland^{10,11}. Its presence is necessary for normal lactation to occur, but what else it does, if anything, is not known. It also has some of the metabolic actions of HGH but is not available in sufficient quantity to test for a growth-stimulating effect in children deficient in growth hormone. Sheep prolactin has 198 amino-acids, of which about a third may correspond to those in HGH; human prolactin has not yet been sequenced.

Growth hormone is present in the human pituitary gland

in much higher concentration than other pituitary hormones. The average gland contains at least 5 mg of HGH, which is about 1% of its whole weight. There is no evidence that this varies with age or sex in adults. The content of children's glands is not known accurately.

Each of the pituitary hormones is secreted in response to the arrival of a releaser substance, manufactured in the hypothalamus and specific for the hormone in question. The releasers are peptides; the structures of several are known and one, the tripeptide thyrotrophin-releasing hormone, has been synthesized and is now in clinical use. Growth hormone releasing hormone (GHRH) appears to be a decapeptide, with a structure common to many species of mammals (Wilbur, Nagel and White, and Schally and Arimura, in ref. 5). The releaser is synthesized in the cell bodies of probably the ventromedial nucleus of the hypothalamus^{12,13} travels down the axons of these cells to the median eminence, enters the blood vessels at the proximal end of the pituitary portal system and thus reaches the anterior pituitary where it acts on the characteristic somatotroph cells (the orangeophil cell of the acidophil class), to cause release and synthesis of GH^{14,15}. Because of the pituitary's high content of growth hormone a good burst of secretion in man, producing a plasma level of 30 μ U/ml. for an hour, probably depletes the gland by only 1 or 2%¹².

The normal stimulus for the secretion of GHRH is not yet known. In monkeys the application direct to cells of the lateral hypothalamus near the ventromedial nucleus of 2-deoxy-D-glucose, which inhibits glucose utilization, stimulates GHRH release (Himsworth *et al.*, ref. 5). Whether this area is the receptor site for more long term regulatory feedback is unknown, however.

A considerable range of stimuli cause an increase in growth hormone in the blood of man; exercise^{16,17}, apprehension and sleep (Eastman *et al.*, refs. 5 and 18–20) are perhaps the most normal of them. The increase during sleep occurs soon after sleep begins, in the slow-wave phase, and is not suppressed by intravenous glucose infusion nor by alpha or beta adrenergic blocking agents²¹. It occurs in children over 5 as well as adults; in younger children the situation is less clear (Illig *et al.*, refs. 5 and 22).

In clinical work a sharp and profound decrease of blood sugar, produced by the intravenous injection of insulin, is regarded as the best stimulus. This is far removed from anything that occurs normally; there has been argument about whether the small decreases in blood sugar that do occur in ordinary circumstances are sufficient to cause secretion of growth hormone, but the balance of evidence is clearly against it (Schewiede *et al.*, ref. 5 and refs. 23 and 24). Hypoglycaemia does not cause secretion of GH in the dog (Irie, ref. 5), cat²⁵, cow (Reynaert, ref. 5), mouse²⁶ or rat²⁷.

Another stimulus used clinically is the ingestion of a large quantity of 'Bovril', a British proprietary meat extract drink²⁸. In children 'Bovril' produces very similar results to insulin hypoglycaemia²⁹, and most, though not all, children regard it as a pleasanter stimulus. In male adults, however, 'Bovril' fails to work unless they are first primed with oestrogen. The intravenous injection of a solution of arginine chloride³⁰ is also used as a clinical test. It also fails to work in non-oestrogenized adult males. The injection of glucagon is a fourth clinically useful stimulus³¹. None of these last three stimuli acts by lowering the blood sugar. It is not known whether GHRH increases in response to these stimuli. A

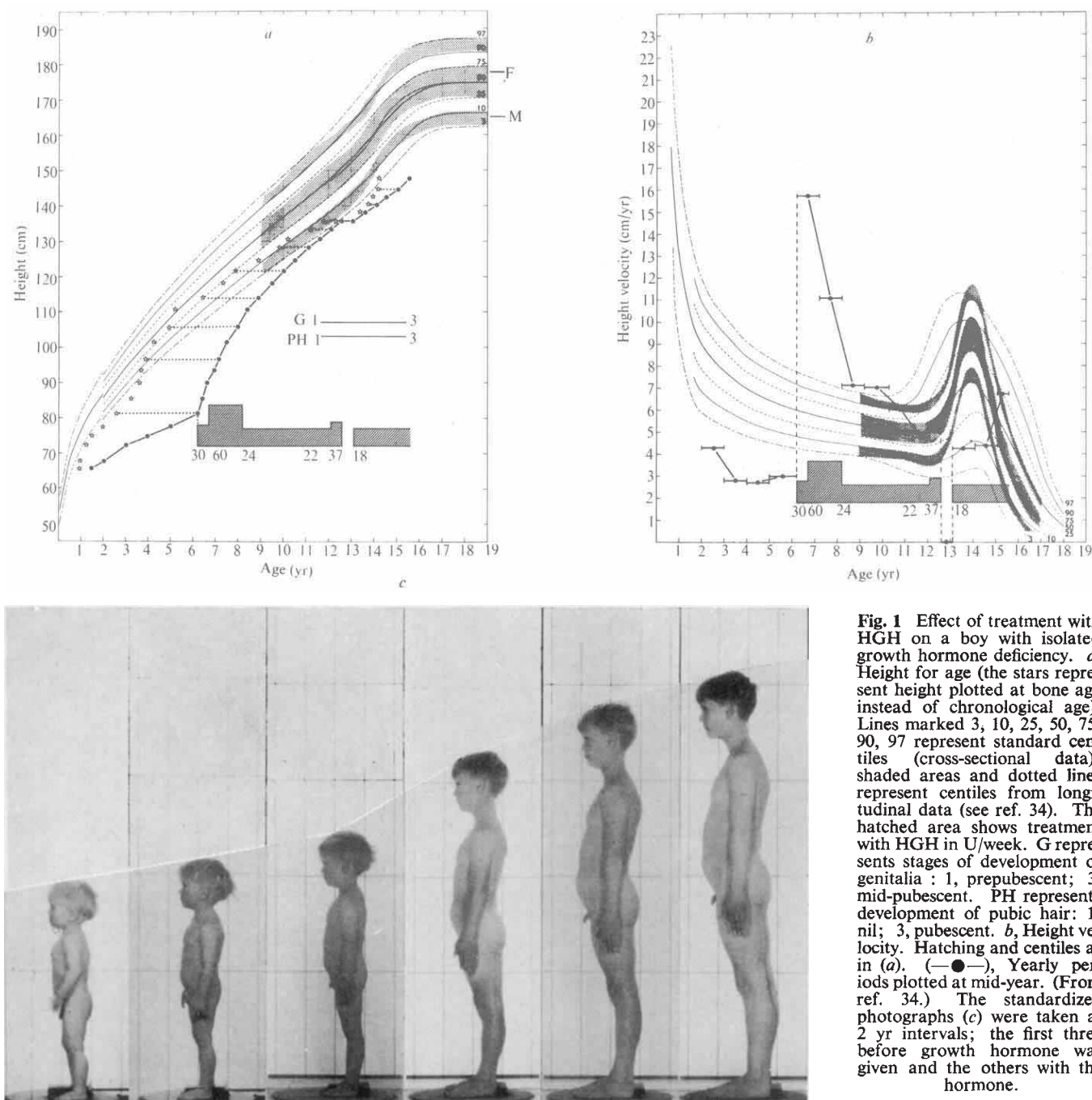


Fig. 1 Effect of treatment with HGH on a boy with isolated growth hormone deficiency. *a*, Height for age (the stars represent height plotted at bone age instead of chronological age). Lines marked 3, 10, 25, 50, 75, 90, 97 represent standard centiles (cross-sectional data); shaded areas and dotted lines represent centiles from longitudinal data (see ref. 34). The hatched area shows treatment with HGH in U/week. G represents stages of development of genitalia: 1, prepubescent; 3, mid-pubescent. PH represents development of pubic hair: 1, nil; 3, pubescent. *b*, Height velocity. Hatching and centiles as in (*a*). (—●—), Yearly periods plotted at mid-year. (From ref. 34.) The standardized photographs (*c*) were taken at 2 yr intervals; the first three before growth hormone was given and the others with the hormone.

decrease in blood fatty acids has also been observed to cause release of growth hormone in normal adult subjects (Quabbe *et al.*, refs. 5 and 32) and has been suggested as the normal stimulus to secretion of the hormone, albeit with a 1 to 2 hour delay. Hansen⁸⁴ has shown that the exercise rise is not mediated this way, and there is evidence⁸⁵ that longer term feedback is not mediated by fatty acid level either. Probably we have to distinguish between short term stimuli and long term modulation of the sensitivity of the receptor site.

Normal Blood Levels and Secretion Rate

Plasma growth hormone is measured by radio-immunoassay, usually with a double antibody technique. The results are reported in terms of units of an international standard preparation kept at the National Institute for Medical Research, Mill Hill.

In the absence of exercise, apprehension, sleep and some other unknown factors, the blood level of immunoreactive growth hormone is generally very low in man (0 to 5 μ U/

ml.). In normal circumstances both children and adults produce a series of bursts of secretion every 24 hours, the number and strength varying in a way we do not understand. (The situation may be akin to that demonstrated for blood luteinizing hormone in cattle, except that the sequence "sight of cow $\rightarrow$ LHRH $\rightarrow$ LH $\rightarrow$ testosterone $\rightarrow$ secretion of seminal fluid" is easy to understand, whereas both cause and result of growth hormone peaking are obscure.)

In adequate insulin hypoglycaemia normal children and adults produce a peak rise to 20 μ U/ml. or above. Patients who have had their hypothalamic-pituitary system severely damaged or who have fully developed isolated growth hormone deficiency (see below) do not rise to over 6 μ U/ml. We think that children with peak values between 6 and 20 μ U/ml. may suffer from a partial hormonal deficiency⁸⁴. The results of the several provocative tests usually agree though there are some 10 per cent of exceptions in which a patient responds to hypoglycaemia, say, but not to arginine⁸⁵. There is no convincing evidence that the level of

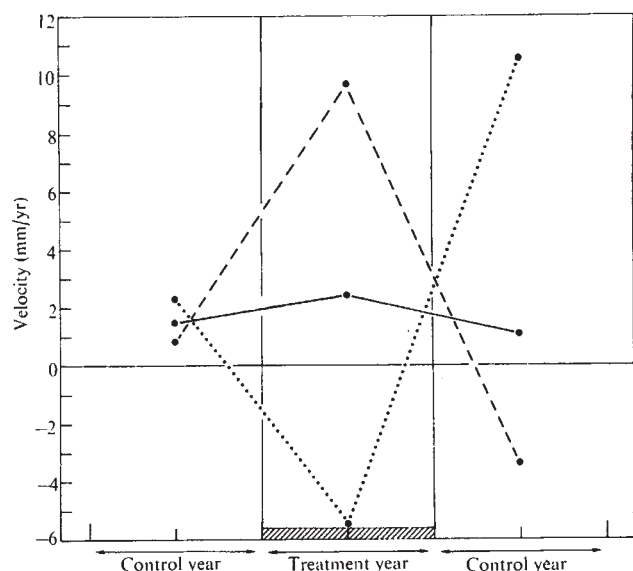


Fig. 2 Mean velocities of widths of bone (—), muscle (---) and fat (...) measured in radiographs of upper arm and calf before, during and after treatment with HGH of seven children with isolated growth hormone deficiency. (From ref. 34.)

the peak response changes during childhood, though some investigators have found that it increases during the adolescent growth spurt³⁶ or on giving testosterone³⁷.

It is not yet possible to calculate 24 hour secretion rates for growth hormone, since the amount excreted in urine is a minute percentage of that produced³². But a small pump has been devised which, strapped on to the back, extracts blood continuously at 1 ml./h through an indwelling arm catheter and stores it over a whole 24 hour period. In this way the average blood level over 24 hours can be estimated, and the secretion rate in four normal women infused with radioactive HGH has been determined as about 0.5 mg/day of pure hormone³⁸. Whether there are age changes in secretion rate is not known.

Somatomedin (Sulphation Factor)

It seems highly probable that growth hormone acts mostly or entirely through the release of a second substance from the liver and possibly the kidney. The substance released was previously called sulphation factor (also thymidine factor, plasma growth factor) because its first demonstrated action was to increase the uptake of radioactive sulphate by cartilage from immature hypophysectomized rats³⁹, growth hormone itself having no *in vitro* action on such cartilage. Very recently the name "somatomedin" has been proposed⁴⁰.

Labelled growth hormone shows early localization chiefly in liver, kidney and adrenal zona glomerulosa in the rat, and not at all in cartilage or muscle⁴¹. Somatomedin is produced by isolated perfused rat livers and possibly kidney slices in a medium containing growth hormone (McConaghy and Sledge, refs. 5 and 87). Partial hepatectomy reduces blood somatomedin level in 4 to 6 hours; as the liver regenerates, the somatomedin level returns to normal⁴⁰.

Somatomedin may be extracted from human plasma as a peptide of molecular weight about 4,000 (refs. 42 and 85). It seems that the species differences characteristic of growth hormone do not exist for somatomedin since plasma from man, monkey, pig, cow, dog and rat is effective in rat, monkey and pig (van de Brande *et al.*, ref. 5).

Hall⁴³ showed that intravenous infusion into children deficient in growth hormone of 4 to 8 IU HGH during 4–5 minutes produced an increase of somatomedin in the blood after about 3 hours, by which time the level of growth hormone had returned to its pre-infusion value. Somatomedin remained elevated during at least 24 hours, which explains the clinical finding that twice-weekly intramuscular

injections of HGH are as effective as daily ones⁴⁴. Children deficient in growth hormone have low plasma levels of somatomedin which, according to Hall and Olin⁴⁶, increase proportionately with HGH dosage in the range of 2–6 IU/week. This agrees with the clinical finding that the height growth response is related to the dose of HGH within this range, while it is not so related in the range above about 15 IU/week. In a single case given 12.5 mg of cortisone before the HGH infusion, somatomedin failed to rise, which may explain the lack of response to HGH of children with short stature due to cortisone administration.

Effects on Muscle and Fat

Fig. 2 shows the effect of giving HGH on muscle and fat growth in the limbs of a child with isolated growth hormone deficiency³⁴. The tissue widths were measured by radiography. HGH increased muscle width velocity greatly, and when its administration was stopped the width actually declined somewhat (that is, showed a negative velocity). Conversely the fat decreased on HGH, and increased again when HGH was stopped. Fig. 3 shows the time-course of the fat decrease, in terms of subcutaneous fat measured by skinfold callipers.

The action of growth hormone to cause multiplication of cartilage cells and skeletal growth is mediated by somatomedin, as is the synthesis of collagen in skin and bone⁴⁵. The same is certainly true of the action on muscle. Salmon and Duvall^{46,47} showed that somatomedin stimulated the synthesis of protein in protein-polysaccharide complexes of isolated cartilage from hypophysectomized rats. They also found that it stimulated the uptake of amino-acids into isolated muscle, and this in a dosage that represented the ordinary serum concentration. Other workers have for many years described stimulation of protein synthesis in isolated muscle by growth hormone itself added to the medium (Turner *et al.*, refs. 5 and 48), but this only in a concentration much higher than that normally seen in blood.

HGH causes an increase of free fatty acids in blood⁴⁹ and a decrease of body fat, and this effect also is probably mediated by somatomedin. At present there is no direct evidence for this. Isolated human subcutaneous adipose tissue, however, failed to release fatty acids when HGH was added; and though isolated rat adipose tissue has been described as releasing fatty acids after growth hormone, the dose was excessively high, as in the case of muscle⁵⁰.

Tests on children deficient in growth hormone are in agreement with this interpretation. When such children, placed in metabolic balance on a constant diet, are given HGH for 3 to 5 days they increase their nitrogen retention more than do normal children in the same circumstances^{51,52}. Patients with an inherited inability to secrete somatomedin when given HGH fail to retain nitrogen in this way (New *et al.*, refs. 5 and 53). They fail also to produce the usual rise in free fatty acids in the blood (Laron *et al.*, ref. 5).

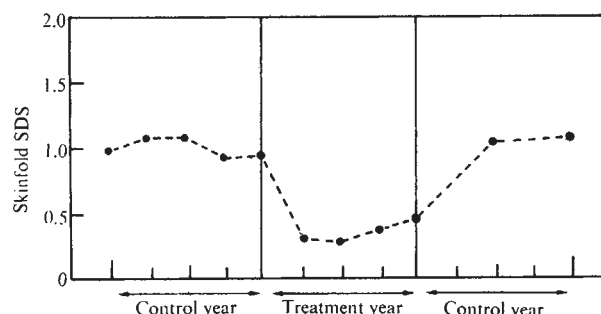


Fig. 3 Subcutaneous fat measured as skinfold by callipers; mean standard deviation score for age and sex at 3-monthly intervals of nine patients with isolated growth hormone deficiency. See text. (From ref. 34.)

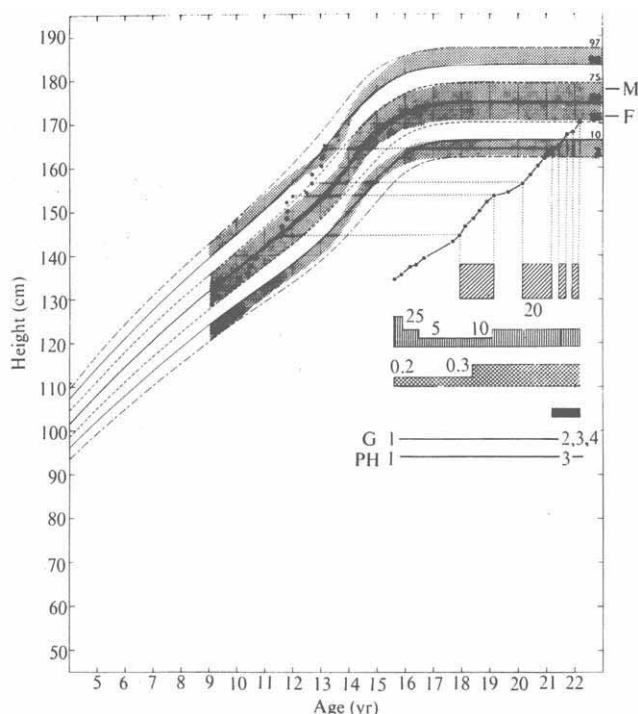


Fig. 4 Treatment of a male craniopharyngioma patient with HGH and other substitution therapy. Height is shown for age (●) and for bone age (*). Hatching represents treatment as in Fig. 1: diagonal hatching, HGH; vertical hatching, cortisone (mg/day); cross hatching, thyroxine (mg/day); black bar, testosterone. G and PH as in Fig. 1.

There may of course be some acute short term effects of HGH not mediated by somatomedin (see discussion in ref. 54). Rabinowitz *et al.*⁵⁵ found that HGH infused into the brachial artery enhanced the uptake of free fatty acids and reduced the uptake of glucose by the forearm muscle. Other short term effects are the decrease in the blood serine occurring within an hour of the intravenous injection of HGH in growth hormone deficiency (Zachmann *et al.*, ref. 5) and the immediate diabetogenic action of HGH infused into adults (Luft *et al.*, ref. 5).

Growth hormone also seems to be involved in the regulation of aldosterone secretion⁵⁶. There is evidence that this action may be via the liver, although HGH does localize in the glomerulosa cells of the adrenal.

Growth Regulation and Catch-up

When a growing animal is starved its growth slows down or stops and when it is allowed food again its growth rate is accelerated above normal, so that the animal catches up to or towards its normal size-for-age curve. The same catch-up growth occurs in children with a growth-retarding disease such as hypothyroidism, cortisol-excess or growth hormone deficiency (Fig. 1) when the disease is rectified². When the animal approaches its normal curve its growth slows down and proceeds along it. A purely hypothetical mechanism has been described for this regulatory phenomenon and the hypothesis extended so that it would explain the mechanism of the normal growth curve, that is, the rapid growth early in childhood, with progressive slowing down. The growth velocity at any time was envisaged as proportional to the mismatch signal generated by the comparison of two processes; a hypothalamic maturation process, little affected by the animals' actual growth and representing a "target", and an "inhibitor substance" produced in the liver proportionately to the amount of tissue actually laid down in the animal, representing "actuality"¹.

There is little factual knowledge about the regulation of growth, but obviously the growth hormone-somatomedin mechanism might be concerned and might clarify or dis-

prove this tentative model. Hall and Olin⁵⁶ write that in growth hormone-deficient children treated with HGH the initial velocity of catch-up growth was linearly related to the concentration of somatomedin in the blood. Above about 15 U/week HGH, however, no further effect on growth velocity occurs. Similarly, if HGH is given to a hormonally normal child, growth rate is not increased. Hall and Olin⁵⁶ found that as the catch-up velocity diminished in the later years of treatment (Fig. 1) the concentration of somatomedin in the blood reduced, although the dose of administered HGH was unchanged. This would seem to imply (1) that the number of binding sites for growth hormone action are fully occupied in the normals (or nearly so), for large doses of HGH do probably cause a short acceleration in normals, followed by a regulatory deceleration when excess HGH is withdrawn⁵⁴, and (2) that the number of sites, or the characteristics of the binding, are somehow related to the size of the animal. There are few published studies of concentrations of somatomedin in normal children in relation to age; the classic paper of Daughaday, Salmon and Alexander⁵⁷ cites the mean for eleven children as 0.84 U compared with an adult mean of 0.78, and Hall⁵⁸ found a mean of 0.94 in eighteen children aged 9 to 13, with an apparent relation between level and growth rate (see also ref. 54).

There may also be a decreasing ability on the part of the tissue to respond to somatomedin, presumably as available "growth-sites" in muscle fibres, for example, become occupied and maximal size is approached. Heins *et al.*⁹ showed that costal cartilages taken from rats nearing the end of their growth period responded much less to a constant dose of somatomedin (from a single human serum) than did cartilage from rapidly growing rats.

This leads to the question of how the secretion of growth hormone is controlled. In protein-calorie malnutrition in children associated with low serum protein levels (kwashiorkor), concentrations of growth hormone were found to be increased (Pimstone *et al.*, refs 5 and 83). This was not due to a low serum albumin concentration, nor probably to the abnormal amino-acid relationship present in this disorder, since infusions of amino-acids failed in most cases to lower the concentration of growth hormone. But there was no increase in basal levels of growth hormone in healthy young adults starved for 4 days (Irie *et al.*, ref. 5), nor in healthy young men kept for 25 days on a protein-deficient but calorically adequate diet⁸⁸. Thus it seems likely that it was factors related to the relative protein growth deficit rather than starvation itself which was stimulating production of growth hormone. There are as yet no published studies of somatomedin in starvation. We may, however, put forward the view that in general the normal long term stimulus to the secretion of growth hormone is a decrease of blood somatomedin, at least in children.

The alternative theory that secretion of growth hormone is inhibited by direct action of the hormone itself on the GHRH centre was proposed by Sakuma and Knobil⁵⁸, who showed that in monkeys a plasma concentration of growth hormone of about 60 μ U/ml., produced by 2 hours of continuous infusion of HGH, abolished any further rise of growth hormone in response to insulin hypoglycaemia.

The somatomedin-feedback view, however, is supported by the experiments of Abrams *et al.*⁵⁹ who showed that repeated injections of HGH into normal young men for 6 days left the subjects temporarily unable to secrete further growth hormone in response to insulin hypoglycaemia. The ability began to return about 12 hours after the exogenous HGH was stopped and was back to normal in about 48 hours. Though Abrams *et al.* do not actually suggest somatomedin as the feedback mechanism the time relations would fit very well with this explanation. Also in favour of this feedback is the high concentration of growth hormone found in children who are unable to secrete somatomedin because of an inherited defect (see below).

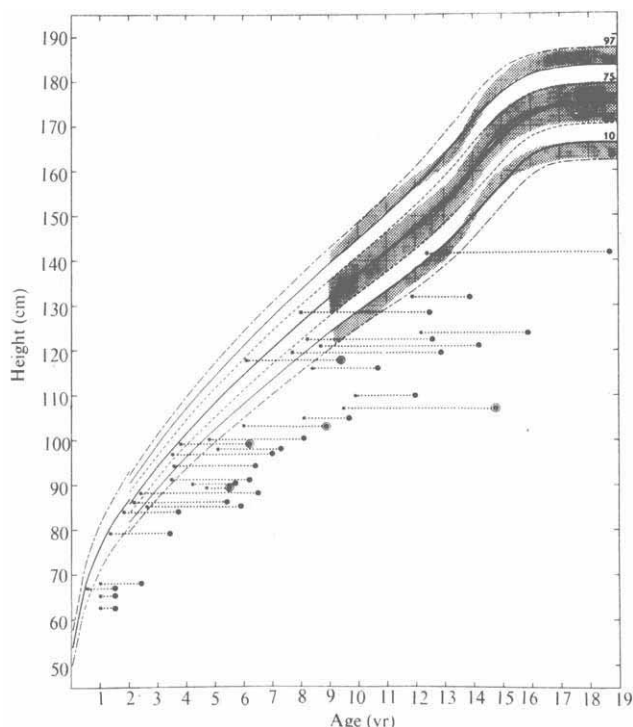


Fig. 5 Height at diagnosis of boys with isolated growth hormone deficiency plotted against chronological age (●) and bone age (★). Partial deficiency cases (○).

The view that the concentration of somatomedin alters the sensitivity of the hypothalamic GHRH site and thus serves to modulate its response to a variety of short term stimuli seems to fit adequately with the known facts. As to the way normal growth is regulated, we are still very much in the dark. Somatomedin might be cast in the role of the peripheral inhibitor in the 1963 model, with the hypothalamic cells altering their sensitivity as the animal ages (as they do to sex hormones at puberty).

Growth Hormone Deficiency

Deficiency of growth hormone may be total or partial and may occur either as an isolated deficiency (hyposomatotrophism) or in association with deficiencies of other pituitary hormones, that is thyroid stimulating hormone (TSH), ACTH or gonadotrophins.

In about one-third of the cases the deficiency follows a lesion of the central nervous system, most frequently a craniopharyngioma. This is a benign tumour, growing close to the hypothalamus and pituitary gland. It usually becomes manifest between the ages of 5 and 15, either through neurological symptoms such as vomiting, failing vision and headache, or more rarely through endocrine symptoms, such as reduced growth rate. The tumour may be removed surgically either in whole or in part. After this there may be any degree of hypothalamic-pituitary deficiency from nil to complete lack of growth hormone, ACTH, TSH, and gonadotrophins. If appropriate amounts of cortisone, thyroxine and growth hormone are given, normal growth is resumed and final height should be normal; at puberty sex hormones are given if necessary (Fig. 4).

The aetiology of the non-tumour cases of growth hormone deficiency is still obscure, but most seem to be developmental in origin and probably represent lesions of the hypothalamus rather than the pituitary. Many cases were previously attributed to birth injury often associated with breech delivery, but there is little evidence that this accounts for current cases in Britain³⁴. Different investigators have different criteria for diagnosing ACTH and TSH deficiency, so the literature records varying proportions of isolated growth hormone deficiency and multiple deficiency^{35,50-61}. Most cases, however

—in our series almost all—seem to have “isolated” deficiency, which term includes children who later, when puberty should start, are found to have gonadotrophin deficiency also. Probably one-third to one-half of the so-called “isolated” cases have gonadotrophin deficiency.

Growth hormone deficiency is not common but there are probably between 100 and 150 childhood cases in the United Kingdom, excluding those caused by tumours. In “isolated” deficiency the child has a normal birth weight, but grows less than normal from shortly after birth. Often his smallness is only remarked, however, when he first goes to school, or when a younger sib overtakes him in height. Curiously enough, most of the patients are boys, who outnumber girls by about 2.5 to 1. Still more curiously, about one-third of the boys have an abnormally small penis and ill-developed scrotum^{34,62} indicating lack of the usual masculinization by androgens *in utero*, though why such a thing should be linked to growth hormone deficiency is not clear.

Some 15% of children deficient in growth hormone have sibs also affected, and 1 or 2% have an affected parent. A clearly genetic form of the isolated deficiency is known, inherited as an autosomal recessive⁶³. (There may also be a very rare dominant form, which would allow Sir Hercules in Aldous Huxley's celebrated story in *Chrome Yellow* to be, as his creator probably intended, a growth hormone-deficient dwarf and not a chondrodystrophic).

Fig. 5 shows the height at diagnosis of a large series of patients from the United Kingdom plotted against normal standards. The stars represent height plotted against bone age, which is always considerably retarded, as shown by the dashed lines. The patients are fat as well as short, and their skinfolds are almost invariably above the fiftieth and usually above the seventy-fifth centile. The diagnosis is confirmed by lack of a normal growth hormone response to one of the stimulation tests.

Treatment

Since 1959 human pituitaries have been collected by pathologists through the United Kingdom, and sent to the Department of Biochemistry at Cambridge where the hormones are extracted under the supervision of Dr Anne Stockell Hartree⁶⁴. The best current extraction techniques obtain about 10 mg of powder per gland, the powder being about half the strength of pure HGH. The material is

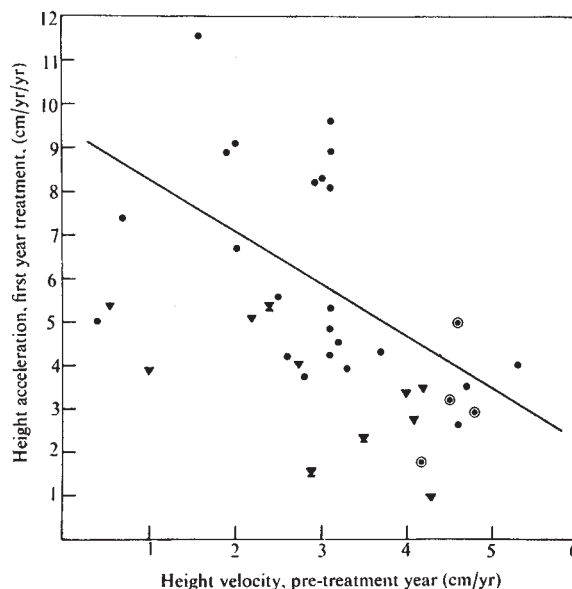


Fig. 6 Relation between height acceleration in first year of treatment (treatment velocity less pre-treatment velocity) and velocity during pre-treatment year. The regression line is only for patients with isolated growth hormone deficiency ($r = -0.58$) (●). Patients with craniopharyngioma are indicated as ▼, and partial growth hormone deficiency as ○.

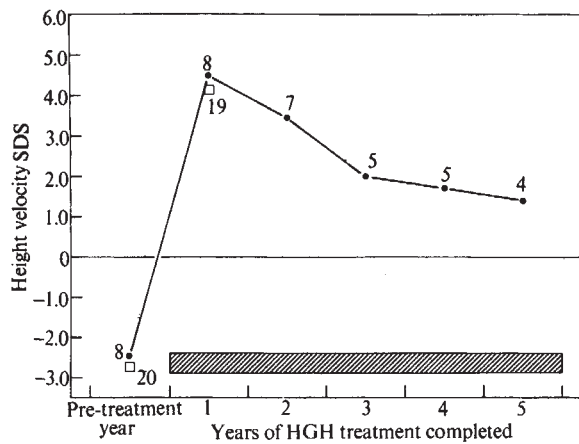


Fig. 7 Height velocity standard deviation score (for age and sex) before treatment and in the first 5 yr of treatment of patients with isolated growth hormone deficiency. Numbers of patients for each plot (●) are marked. □, Total number of patients in group.

made available for treatment in a National Clinical Trial of HGH, carried out by the Medical Research Council. Supplies at first were severely limited, but thanks to the extraordinary degree of cooperation of pathologists in the United Kingdom 60,000 glands a year are currently being collected, which yields enough hormone to treat some 500 to 600 children. On present evidence this is sufficient to treat all children in the UK who would benefit, a situation also obtaining in Norway, Sweden and Australia. The material is given by intramuscular injection of either 5 or 10 U twice a week. There are no known side effects, even from large doses. Very high doses in certain other species have a diabetogenic effect⁶⁵, but this does not occur in man or the rat⁶⁶.

The conditions of the trial demand that the patient have a full year of accurate measurements of growth before starting treatment. The response at the end of 1 year of treatment is evaluated (lesser periods leading to error because children grow much faster at some times of the year than others⁶⁷). If the change in velocity of height growth is significant and substantial (more than 3 cm/year increase) the treatment continues.

A typical response is shown in Fig. 1. The acceleration is greatest in the first year and subsequently becomes less. The first year acceleration is quite closely related to the velocity in the pre-treatment year, as Fig. 6 shows; the children with only partial deficiency respond less but significantly, and should certainly be treated⁸⁴. Fig. 7 shows the gradual fall-off in response as the patients approach normal limits.

The treatment should probably be continuous until growth has ceased. There is evidence, not yet conclusive, that the adolescent spurt in growth^{68,69} depends on both growth hormone and androgens for its full development^{34,37,70}. In the Medical Research Council trial a controlled test of this is being undertaken. In patients who have gonadotrophin deficiency, testosterone or oestradiol is given when the full pre-adolescent growth potential has been exhausted (and not before: giving anabolic, testosterone-like, steroids to these patients is strongly contraindicated and may do irreparable damage by causing their bones to mature, thus rendering them insensitive to HGH). Patients deficient in growth hormone are always delayed in their growth and respond to HGH at quite advanced chronological ages, provided their bone age is not above about 14 "years" in girls and 16 in boys. (Comprehensive accounts of treatment have been given in refs. 34, 35, 59, 61 and 71.)

Though some patients treated with HGH develop very low levels of antibody which have no effect on their growth response, a few generate high levels and stop growing^{73,78} (Fig. 8). The reason is unknown, but it is good to note that

the incidence has declined in recent years, which suggests that it was due to the material or its carrier. In the UK series there have been four such children, but none in the past 6 years.

Transient Deficiency and "Psychosocial Short Stature"

There may also be transient deficiencies of growth hormone secretion. Some boys with delayed puberty may suffer from this; when puberty starts the deficiency rights itself; it need not be treated⁷⁴. There is also a category of children who are small for emotional reasons, and who have a typical catch-up, looking just like a response to growth hormone, when taken from their surroundings and placed in a foster home or boarding school. These children may be fat and so far as can be determined do not have calorie deficit^{75,76}. They do not secrete growth hormone in response to insulin hypoglycaemia or 'Bovril' in their home surroundings, but when removed from them the response usually reappears⁹¹. Presumably they inhibit their GHRH under psychological stress. However, we have treated three of them with exogenous HGH while they stayed in their home situation, and surprisingly obtained no catch-up at all³⁴.

Somatomedin Deficiency

There are a few patients known who resemble children who are seriously deficient in growth hormone, but whose levels of the hormone are normal or even high, sometimes without even a stimulus. This syndrome is due to an autosomal recessive gene and appears to be commoner in middle eastern Jews than other populations. At first it was thought that these patients responded to exogenous HGH and hence that they had a defective growth hormone molecule^{77,78}, but later studies have shown that they suffer from somatomedin deficiency and do not in fact grow when given HGH^{34,79}.

Excess of Growth Hormone/Somatomedin

While pituitary gigantism, believed (perhaps wrongly) to be due to high growth hormone, is exceedingly rare, acro-

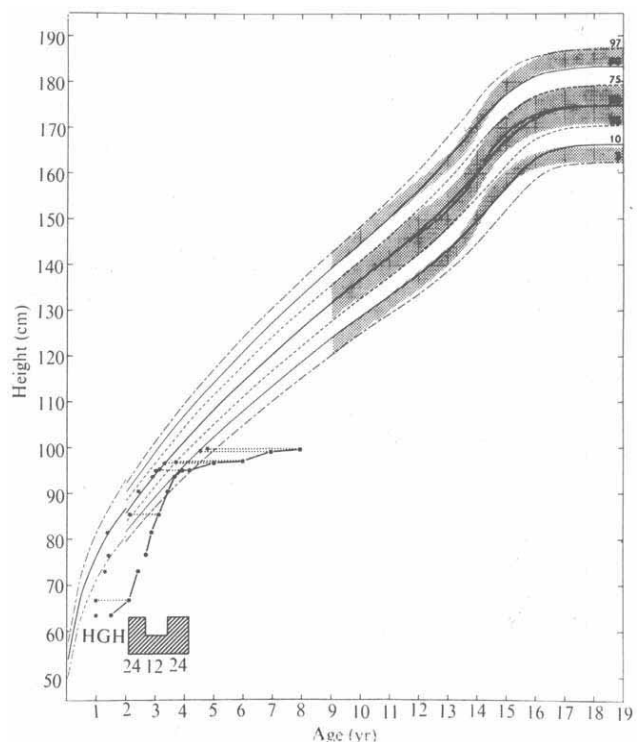


Fig. 8 Effect of development of antibodies on height response to HGH. Antibodies developed in high titre just before treatment was discontinued. Hatching represents treatment as in Fig. 1.

megaly, the adult equivalent, is not. Though often associated with a tumour of the pituitary, it is now thought that it may usually start as a disruption of the hypothalamic control, with chronically elevated levels of growth hormone⁶⁰ and, in the acute phase, high somatomedin⁶¹.

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Extragalactic X-ray Sources

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The extended X-ray sources associated with the Virgo, Perseus, and Coma clusters of galaxies can best be explained as a result of the Compton scattering of relativistic electrons (generated in the radio sources which are present in each of these clusters) on the microwave background radiation. The same physical process involving microwave infrared or optical photons generated in the nuclei of active galaxies may account for the more compact X-ray sources. Thermal bremsstrahlung of hot gas in clusters of galaxies is a less likely source of X-rays.

RECENTLY several extragalactic X-ray sources have been discovered and a few have been identified with optical or radio sources. Although the observational results are still scanty, the sources seem to fall into three classes: first, normal galaxies similar to our own in which we have every reason to believe that the X-ray emission originates in a number of powerful, discrete objects, perhaps binary stars, and in supernova remnants. Second, galaxies and at least one QSO (3C 273) which are known to be powerful nonthermal sources of radio and/or infrared flux. It is generally accepted that these objects have intensely active nuclei¹ and one mechanism which may give rise to the X-rays is the Compton effect involving the high energy electrons and radio or infrared photons generated in the nuclear regions of the galaxy². Third, the extended X-ray sources with sizes ranging from $\sim 10^5$ to 10^6 pc which seem to be centred on clusters which contain active galaxies. Here we discuss the mechanisms which may be operating in the second and third categories of sources.

We first consider extended sources whose X-rays may arise from synchrotron radiation or Compton scattering of fast electrons on magnetic fields and radiation filling the intra-cluster medium, by thermal bremsstrahlung of hot intergalactic gas, or by many as yet unresolved sources distributed over a large volume. The mean X-ray flux detected from normal galaxies is insufficient to account for the observed X-ray fluxes from Coma and Perseus by at least an order of magnitude³, and little is to be gained from postulating an abundant class of still weaker sources. We thus consider only the diffuse sources first mentioned. Unfortunately, it is not yet possible to distinguish between a thermal or nonthermal origin for the emission from these sources from the spectral information available³.

Because the generation of synchrotron X-rays requires very strong magnetic fields and/or very high energy electrons with very short lifetimes, this mechanism cannot be operating in extended sources unless such sources are made up of many very small local generators of particles and magnetic fields. In that case high resolution studies would show that a source

is made up of small components. At radio frequencies, studies of the Coma cluster⁴, for example, show that many more sources than the visible galaxies are required to explain the apparently smooth radio emission. At X-ray energies, however, we are many years away from such an observational test. Without prejudice, and for the time being, we exclude this possibility in discussing extended sources.

Thermal Bremsstrahlung

The idea that extended X-ray sources have a thermal bremsstrahlung origin is linked to the idea that an intergalactic gas may be present both in clusters and throughout the universe. Over the past decade there have been attempts to discover intergalactic gas, either hot or cold, but they have all so far led to null results⁵. Thus the attribution of X-rays to a hot gas is at present the only evidence for such gas. Henry⁶ has set severe new limits on the clumpiness and temperature of any such gas on the basis of an upper limit on the Lyman α flux from the Coma cluster. There has been a tendency to explain the observations as evidence for the presence of a hot gas, which might also provide the "missing mass" needed to bind the Coma cluster⁷⁻⁹. But both the X-ray intensity and the Ly α limits have shown that, even if the hot gas is responsible for the X-ray flux, the amount of mass present in this form is negligible and can have nothing to do with the dynamics of the cluster.

What evidence do we have which bears on the hot gas hypothesis for the three sources in clusters which are reported to be extended, namely those associated with the Coma, Perseus and Virgo clusters? Such gas, if it is present, may be intergalactic gas which has been accreted by the cluster¹⁰, or it may be gas which has been ejected from galaxies in the cluster and is being swept out of the clusters^{11,12}. In either case we might expect that the X-ray emission is correlated with the total number of galaxies in the cluster and its dynamical state. The equilibrium temperature distribution of the gas and hence the X-ray energy spectrum will depend on many parameters including, for example, the accretion rate in one case, and the rate of ejection of gas from galaxies in the other; but if we could measure the X-ray spectrum through a wide energy band, it would be surprising to find that clusters with very different optical and dynamical characteristics do not radiate at very different rates.

The X-ray luminosities Coma : Perseus : Virgo are in the ratios 20 : 40 : 1, and their X-ray diameters are in the ratios 3.6 : 3 : 1, corresponding to approximately constant volume emissivity¹³. It is well known, however, that their optical properties and dynamical characteristics are very different. The Coma cluster is a rich, highly centrally condensed, relaxed system for which virial theorem calculations suggest that the total mass required to bind the system is only a factor of 3 to 5 more than the mass that can be estimated to be present in the form of normal galaxies^{14,15}. Because the distribution of the galaxies suggests rather strongly that the system is bound, this has led to a search for the missing binding mass.

The Perseus cluster, in contrast, is a highly irregular cluster. The bright galaxies form a prominent chain including NGC 1275, NGC 1272 and IC 310. The velocity dispersion of the constituent galaxies is the largest known in any cluster and application of the virial theorem suggests that either a very

large fraction of the mass is hidden or the system has positive total energy¹⁶. The asymmetrical distribution of the central bright galaxies suggests that the cluster is unstable, though Oort¹⁷ has argued that such formations could be the result of comparatively recent condensation out of a hypothetical intergalactic gas.

The Virgo cluster is a rich but highly irregular cluster¹⁸ consisting of large numbers of both spiral and elliptical galaxies¹⁹ which also can only be stable if a large amount of mass—perhaps ten times the mass in visible galaxies—is present.

We stress that these clusters, although they may be of comparable size, have very different dynamical characteristics from one another, and there seems to be no correlation between their very different dynamics and galaxy populations and the rates of X-ray emission. As we shall describe later, they have more similarities in their radio properties.

We now consider in more detail what we expect if hot gas were responsible for the X-ray emission from the Coma cluster, making the reasonable assumption that it is a gravitationally bound stable system. We suppose that the temperature is characterized by the root-mean-square dispersion velocity of galaxies in the cluster ($kT \approx 4\text{--}10$ keV). We then expect, *a priori*, that the spatial distribution of the gas will follow that of the galaxies provided that the gas makes a negligible contribution to the mass. That is the case whether it was accreted from outside the cluster or was ejected from galaxies in the cluster. In the inner part of the cluster the distribution of the galaxies follows that of an isothermal gas sphere²⁰ so the gas should follow a similar distribution. Bearing in mind that the emission $L_x \propto n_e^2 T$ with constant T throughout the cluster and using the structural parameters for the inner part of the Coma cluster as given by Zwicky²⁰, we find that the X-ray source to half intensity should appear to be $\lesssim 10$ arc min in diameter (depending on the exact detector parameters) as compared with the reported diameter of 45 arc min. This is certainly a simplified argument, but it clearly does not support the hot gas model.

Compton Scattering

Because we have independent evidence for the existence of microwave background radiation, and large fluxes of relativistic electrons are known to exist in extended radio sources, it is natural to suppose that extended X-ray sources may arise and co-exist with the radio sources.

We have shown²¹ that the extended X-ray source in the Coma cluster could be generated by the Compton process, because the cluster contains an extended radio source of ~ 40 arc min diameter. A dynamical model of cluster winds was constructed, and on this basis the steep low frequency radio spectrum of Coma was interpreted as evidence for the trapping (or slow leakage) of electrons from the cluster. We also predicted that the radio-emitting cluster Abell 1367 (and others)

would turn out to be an extended X-ray source. This prediction has since been confirmed by observations with the UHURU satellite¹³. Bridle and Feldman²² used the list of sources found by the UHURU satellite²³ to identify the following radio sources: 3C 66 centred on Abell 347; 3C 264 centred on Abell 1367; and Coma C centred on the Coma cluster as X-ray sources. But Gursky *et al.*¹³ have described their observations of extended X-ray sources and have argued that the most powerful sources arise in the richest clusters of galaxies. We have therefore looked for correlations between powerful X-ray sources and rich clusters, and between powerful X-ray sources and extended radio sources.

Table 1 Abell Clusters with $D \leq 3$, $R = 2$

Abell No.	Radio flux (230 MHz) (10^{-26} W m ⁻² Hz ⁻¹)	X-ray flux (2–10 keV) (10^{-11} erg cm ⁻² s ⁻¹)	Distance class
168	0.16		3
401 (0258 + 13)	0.52	5.1	3
426 (0313 + 14)	13.00 ($\sim 40'$)	68 ($\sim 36'$)	0
754	0.40		3
1035	0.12		3
1367 (1144 + 19)	5.90	6.1	1
1656	0.74 ($\sim 40'$)	21 ($\sim 45'$)	1
1904 (1257 + 28)	0.12		3
2065	< 0.10		3
2151	1.20		1
2199	3.55		1
2255	0.80		3
2256 (1706 + 78)	0.70	5.4	3

D and R are Abell's distance and richness classification numbers. Angular sizes are included in parentheses next to fluxes. UHURU source names given adjacent to Abell numbers where known. Cluster, X-ray, and radio data taken from the Abell²⁵, UHURU²³, and Fomalont and Rogstad²⁴ catalogues, respectively.

If the X-rays are emitted primarily by thermal bremsstrahlung rather than by Compton scattering, we expect the former correlation to be the stronger. All five Abell clusters identified by Gursky *et al.*¹³ as X-ray sources have been classified in the richest class 2 (Table 1). Presumably these are also those clusters most likely to emit thermal X-rays. But the radio survey of Fomalont and Rogstad²⁴ shows that all of these clusters contain sources of radio emission (see Table 1). Both hypotheses are statistically credible, but we find several other radio emitting Abell clusters whose positions may be consistent with UHURU X-ray positions, most notably Abell 347 and Abell 496 (Table 2). Neither of these has richness class 2. Further, ASE 1348 + 211 may be associated with Abell 1795, a strong radio source, but at distance class 4. Until better X-ray positions are determined, however, identifications must be very tentative.

In Table 1 we have listed all of the clusters of richness class 2 in Abell's catalogue²⁵ out to a distance class 3 or less. On

Table 2 Possible Identifications of Some Extragalactic X-ray Sources

UHURU No.	Proposed identification Optical name	Radio name/No.	Radio flux (v[MHz]) (10^{-26} W m ⁻² Hz ⁻¹)	X-ray flux (2–10 keV) (10^{-11} erg cm ⁻² s ⁻¹)	D	R	Distance* (Mpc)
0227+4	Abell 347	3C 66	9.2 (230)	8.5	1	0	129
0426-10	Abell 496		1.47 (230)	3.9	3	0	
0447+44		3C 129	21 (178)	10.2	?	?	
1228+12	Virgo Cluster or M87 Halo	3C 274	970 (178)	37.4	0		15
1247-41	NGC 4696	PKS 1245-41	7.3 (408)	10			56
1322-42	NGC 5128	Cen A (MSH 13-42)	8,700 (85)	10			4
1348+24	Abell 1795		1.02 (230)	6.5	4	2	
1957+40		Cyg A (3C 405)	8,100 (178)	8.7			342

* Except for M87 and NGC 5128 distance has been obtained from the published redshift and an assumed value for the Hubble constant of $50 \text{ km s}^{-1} \text{ Mpc}^{-1}$.

the basis of either the radio criterion or the richness criterion, we expect that Abell 754 and 2255 will be found to have X-ray fluxes comparable with Abell 401 and 2256; similarly Abell 2151 and 2199 should appear somewhat brighter, perhaps with fluxes comparable with Abell 1656 and 1367. But Abell clusters 168, 1035, 1904 and 2065, which are optically similar to the already detected sources Abell 401 and 2256, are extremely weak radio sources and, on the basis of the Compton model, should have fluxes $L_x \leq 10^{-11}$ erg cm $^{-2}$ s $^{-1}$ and should be undetectable in the current surveys.

Unfortunately, without more detailed radio spectral information about these clusters, it is not possible to make any quantitative predictions of the associated X-ray fluxes. That is, given a narrow band of observed radio emission of intensity L_r produced by relativistic electrons radiating in a magnetic field H , the corresponding X-ray flux produced by scattering on the microwave background of temperature T_b and energy density ρ is given by²⁶

$$\frac{L_r}{L_x} \approx \frac{H^2}{8\pi\rho} \left[\frac{2 \times 10^4 T_b}{H} \right]^{\left(\frac{3-m}{2}\right)}$$

where m is the electron spectral index. By analogy with the Coma cluster, if other clusters have intergalactic magnetic fields with $H \approx 10^{-7}$ – 10^{-8} gauss, those electrons radiating at 230 MHz would produce 10^2 – 10^3 keV X-rays on the microwave background. Thus in extrapolating the radio data to much lower frequencies (and lower electron energies) the estimate of L_x in the narrow observing band 2–10 keV is very uncertain. If the nearby rich clusters which have not been looked at so far turn out to have undetectable X-ray fluxes, that will further weaken the case for the presence of hot intergalactic gas in them. Conversely, the detection of the nearby radio emitting clusters with richness class 0 or 1 (for example, Abell 278, 569) would further support a Compton origin for cluster X-ray emission.

Other Extragalactic X-ray Sources

It is necessary to say something about other extragalactic X-ray sources (Table 2) in order to clarify the nature of those known to be extended.

M87 The linear diameter of the source around M87 seems to be significantly smaller¹³ than that in the Coma and Perseus clusters. Further, the limits recently set on the low-energy X-ray flux from the Virgo region²⁷ may indicate that the source is self absorbed, suggesting a fairly high density of gas in or near the source. It is possible that this source is simply associated with the halo of radio emission about M87 and has nothing to do with the Virgo cluster as a whole.

3C 129 and 129.1 The nature of the cluster in this region is not known, nor do we have any information on the extent of the X-ray source. Again, there is no reason to argue that this is X-ray emission from the cluster. Instead it may simply arise from the extended radio source in that region, or it may be a point source generated in the active galaxy which is responsible for the radio source.

NGC 5128 This galaxy has given rise to a powerful and very extended radio source, Centaurus A²⁸, but the X-ray flux from the extended radio emitting region is very weak^{27,29–31}, and the X-ray source is very likely to be confined to the optical galaxy²⁷. This sets limits on the physical conditions in the radio region^{29,31}.

NGC 4696 This is a radio galaxy in a rich cluster at a distance comparable with the distance of the Perseus cluster. The radio source has a small angular diameter 0.6 arc min (ref. 32), and nothing is known about the angular diameter of the X-ray source. So the X-ray source may be associated with the radio galaxy and not with the cluster as a whole.

In all of these objects the X-ray emission either is not observed to arise in a very large extended region, or is known

to be restricted to the radio source or the galaxy. This leads us to consider the possibility that most of the extragalactic X-ray sources may turn out to be associated with active radio galaxies or galaxies which have active nuclei, that is, objects in category 2. At present only three extragalactic sources have been stated to have large angular sizes and the sizes of all of the other sources listed are not known.

Cygnus A has been tentatively identified by Gursky *et al.*¹³ on the basis that this well known very powerful radio source lies in the large error box assigned to the X-ray position. Because there are a number of galactic X-ray sources in this direction, much more precise positional agreement between the X-ray position and the radio position must be obtained before this identification can be made to look really plausible.

Conclusions

If X-ray sources have linear dimension $\sim 10^6$ pc, the X-ray emission probably arises through Compton scattering of fast electrons on the microwave background radiation. The electrons may be generated in many galaxies in such clusters, rather than from one or two extremely active galaxies. If that is the case, it is possible to account for the intensity of the X-ray background radiation with the following assumptions: the electron production per galaxy is the same for all galaxies, independent of their clustering tendency; and the rate of electron generation per galaxy is approximately equal to the value required to explain the X-ray luminosity of the Coma cluster²¹.

The observations made so far give little evidence in support of the idea that X-ray emission from clusters is a result of the presence of a hot intergalactic medium filling the clusters.

It is entirely possible that many extragalactic X-ray sources with small or large linear dimensions arise because a galaxy or QSO is generating large fluxes of relativistic electrons in its nucleus. If it can be shown that the X-ray source has a very small angular diameter and coincides with the nucleus of the galaxy, it seems likely that the X-rays can be generated by Compton scattering of the electrons with the nonthermal radio, microwave, or infrared photons generated in the nucleus. If the source is large, then it is likely that the X-rays are produced by Compton scattering of electrons generated by the galaxy which leak out and interact with photons of the microwave background radiation field.

In this discussion we have accepted at face value the tentative identifications of X-ray sources which have been made by the observers, and we have added a few of our own. But it should be remembered that the positional accuracy which can be obtained is very poor at present. Although it is natural to attempt to identify X-ray sources with comparatively rare classes of objects such as rich clusters of galaxies or powerful radio sources, the possibility that many X-ray sources will turn out to be associated with other hitherto unrecognized classes of objects is certainly not excluded.

By analogy with the developments in radio astronomy, certainty of identification will only come when X-ray source sizes and positions can be measured with comparable accuracy to those currently used in optical and radio astronomy.

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Collagen-like Structures in Ordovician Graptolite Periderm

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Electron microscopic studies of skeletal periderm of 450 million year old graptolites (Hemichordata) reveal a morphologically well-preserved fibrous material which resembles collagen in association with polysaccharide. The cortical fibrils, organized into lamellar plies, show a rough periodicity, a central "core" and helical structure, all of which can be related to extant collagens.

THE extinct Palaeozoic colonial graptolites, together with some bacteria, many plants and some arthropods, form a large segment of the fossil record that is relatively common but completely devoid of so-called mineralized "hard parts". The composition of the skeletal periderm of graptolites is little known and the few published electron microscopic studies¹⁻³ of graptolites were not directed to this problem. Foucart *et al.*⁴ have eliminated chitin as a possibility and have also reported finding no evidence of cellulose. We report here that the thecal wall periderm of graptolites was constructed of polysaccharide-associated collagen-like fibres.

By analogy with living representatives the commonly preserved parts of fossil plants and arthropods are usually inferred to have been cellulosic and chitinous respectively. In the case of the graptolites such inferences do not apply because the taxonomic affinity of this group is not clearly established and skeletal substances within the present-day representatives of Protochordata—with which graptolites are usually associated—are varied with known occurrences of cellulose and keratin as well as collagen. The Pterobranchs *Rhabdopleura* and *Cephalodiscus* are presumed to be the closest living relatives

of the graptolites, but the composition of the organic skeleton of neither is known in detail except that chitin and cellulose have been ruled out⁵. The coenecium of *Rhabdopleura* is thought to be at least partly keratinous⁶.

Several rhabdosome fragments of the Upper Ordovician dendroid graptolite *Dictyonema* sp.⁷ were etched from limestone (Baltic glacial erratic boulder No. 0.62 in the collection of the Institute of Palaeontology, Warsaw) with dilute acetic acid, rinsed in distilled water and embedded in 'Durcupan' after dehydration in graded alcohols and propylene oxide. Ultrathin sections of varying thicknesses were studied unstained in a Philips EM-200 transmission electron microscope which was operated for optimum contrast at 40 kV with a 25 μ m objective aperture.

The thecal wall which housed the zooids of mature graptolites consists of two basic peridermal tissues⁸: (1) a fusellar tissue layer constructed of semiannular or annular fusiform growth bands; and (2) a cortical tissue layer which is an outer laminated component. There is also an outer membrane to the fusellar layer which also serves to delineate and separate each fusellus⁸. This basic structure, originally described in the light microscope, is confirmed by electron microscopy (see Fig. 1). The periderm is dominated by fibrous material of two basic types: (1) coarse oriented fibres and (2) thin, spongy fibres. In general, the coarse, oriented fibres occur within the cortical layer and the finer, spongy fibres occur in the fusellar layer, but there are exceptions. The coarse, fibrous material occurs in bands with each band separated by a membranous sheet to give the characteristic laminated structure observed in the cortical layer by light microscopy. Within each band the fibres are closely packed and share a common orientation, but between bands there is a change in orientation (Fig. 2). In cross-section the coarse fibres appear roughly circular in outline and usually display a central dot or "core". In longitudinal and oblique views a periodic structure and the central core region are evident. The period repeat is somewhat

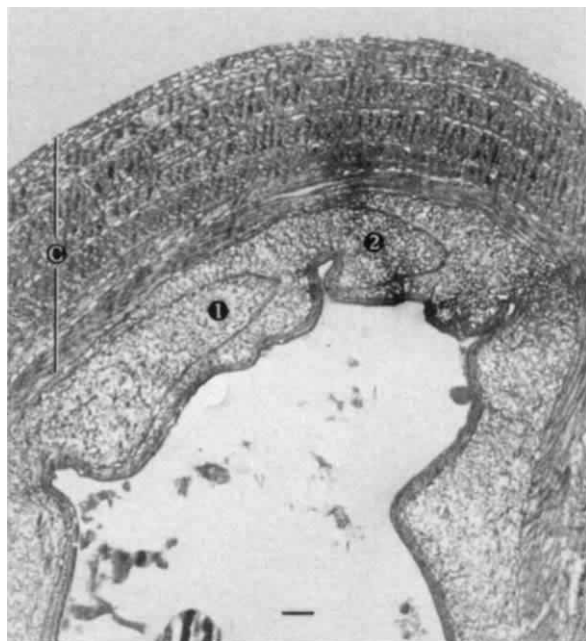


Fig. 1 Electron micrograph of sectioned periderm of *Dictyonema* sp. showing the outer lamellar cortical component (C) and fuselli (1, 2) of the inner fusellar layer. Scale: 1 μ m.

variable but averages about 800 Å on sections studied with internal calibration provided by polystyrene latex spheres.

The structure and organization shown in the electron microscope by the cortical component of the graptolite periderm superficially resemble the structural protein collagen, as is shown in Fig. 3 where a section through the sclera of the rabbit eye showing the layers of collagen fibrils is compared with graptolite cortical tissue (the magnifications of the two photographs are identical). This organization of alternating fibrous plies is relatively common in collagenous structures from many organisms. In addition to the ocular structures reported by Jakus⁹, similar arrangements occur in basement lamellae of larval amphibian skin¹⁰ and in adult lamprey skin¹¹. In spite of the similarities between graptolite and vertebrate tissues shown in Fig. 3 there are also important differences. In graptolites each layer of fibrils in the cortical tissue is separated from the next by a membranous structure which is not seen in most other collagenous tissues with a similar construction. The period repeat of native type vertebrate collagen, although quite variable, is closer to 600 Å than to 800 Å. A similar banding between collagen fibrils can be seen in decalcified dentine of Pleistocene age¹² and, crudely, in decalcified Jurassic bone material¹³. The presence of a more or less periodic banding between collagen fibres is unusual in conventionally stained material although it has been observed in limited situations in some ocular tissues (personal communication from M. A. Jakus). Electron microscope techniques¹⁴⁻¹⁶ for the staining of acidic mucopolysaccharides with ruthenium red, however, have revealed collagen fibrils (ref. 16, Figs. 5-7, 21) in which there is a periodic arrangement of the ruthenium red positive material between fibrils. Highton, Myers and Rayns have applied¹⁷ ruthenium red techniques to synovial tissue collagen, and have also found ruthenium red positive material transversely across the fibres and extending out for short distances from the fibres. Utilizing a model proposed by Mathews¹⁸ they state: "The short side projections of ruthenium red positive material shown on collagen fibres . . . might be parts of protein-polysaccharide complexes in parallel alignment with fibres and helping to hold the component collagen fibrils in place."

The general association of collagen with mucopolysaccharides is well known although the degree of relationship is variable¹⁹⁻²¹. But in comparing these data with those of grap-

lite cortical material it is of interest to note that Hunt has pointed out²¹ that ectodermal collagens usually have higher carbohydrate contents than mesodermal collagens. Furthermore, Rudall²² has observed that a higher carbohydrate content has a tendency to obscure the banding of the collagen fibrils themselves and that there may be no banding at all in some cases or an unusual banding associated with a narrow core in the fibre.

A narrow core is shown in graptolite cortical fibrils and is of special interest because it, too, is an additional feature discussed in the polysaccharide-stained collagens of Luft¹⁶. Here, ruthenium red positive central dots are shown in transverse sections. Several other occurrences of collagen fibrils with central dots or cores have also been pointed out^{11,22,23}, but in these instances the central dot appears as a core because conventional protein stains were used in each case. The central dot or core in these collagens compares with that seen here in graptolite cortical fibrils.

Helical structures are also observed in graptolite fibrils (Fig. 4) and they are usually associated with the central core area. These structures are associated with many fibrous proteins including collagen and, although we know of no instances relating helices to a central dot, the presence of the structures throughout the fibrils of native collagen has been demonstrated by Bouteille and Pease²⁴, who have emphasized the beaded and helical nature of filaments embedded in a carbohydrate matrix.

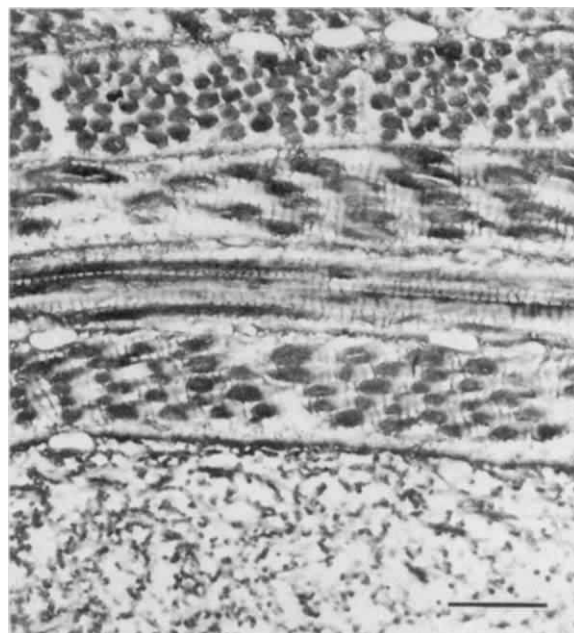


Fig. 2 Fine structure of fusellar meshwork (below) and cortical plies of *Dictyonema* sp. The coarser cortical fibrils show periodic structures as well as central dots and each ply is separated by membranous material. Scale: 1 μ m.

In extant organisms central dots, helical structures, the presence or absence of a periodicity or even the value of the periodic repeat itself are not by themselves usually sufficient to define the fibrous material involved as a collagen, and X-ray diffraction data and amino-acid analyses are usually required for an unequivocal identification. Because the graptolite material under study here is about 450 million years old and is preserved as a carbonized fossil it is unlikely that the original amino-acids of a proteinaceous component will be found unaltered. Nevertheless, by courtesy of D. Von Endt and P. E. Hare, we analysed the 6 M HCl hydrolysable material by high sensitivity ion-exchange column chromatography, taking care to minimize contamination. As expected, very

little of the periderm now seems to be protein and those amino-acids found in low quantities provide little evidence for or against collagen. Although glycine and proline are present, there are no signs of the amino-acids, hydroxyproline and hydroxylysine, which are critical for collagen identification, are rapidly degraded in fossil material²⁵⁻²⁷ and are found only in small quantities even in geologically recent fossil bone from Pleistocene deposits²⁸.

Because wide angle X-ray diffraction data from collagens (or any protein) are dependent on the rigid polypeptide chain configurations these data suggest that the probability of finding positive results from the graptolite material would be very low. Nevertheless, a sample of the intact periderm was submitted to wide angle X-ray diffraction using Ni-filtered Cu radiation, but, except for some lines from adventitious mineral matter, the material gave no other data. All attempts to stain the ultrathin sections for electron microscopy with phosphotungstic acid or uranyl acetate were negative. These results indicate that the biochemical preservation of the periderm is poor in comparison with the good morphological preservation, a conclusion which has been reached in studies of other fossil organic materials²⁹⁻³².

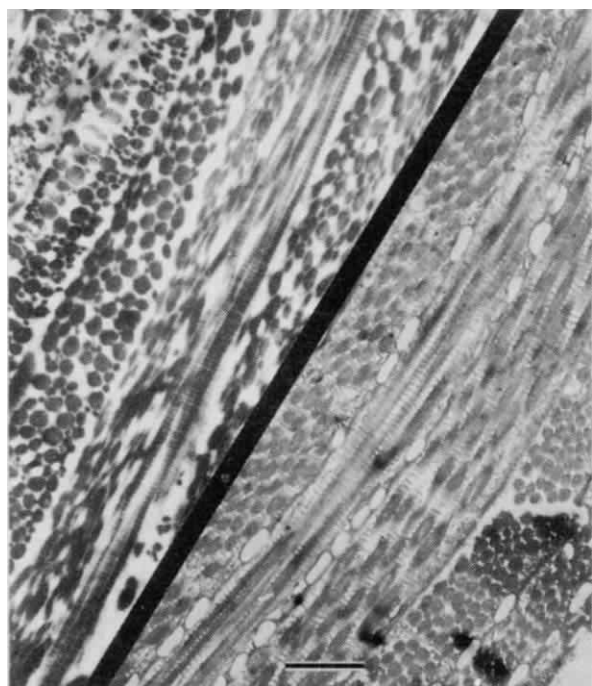


Fig. 3 Comparison of collagen fibrils in the sectioned sclera of the rabbit eye (upper left, courtesy Jakus, M. A.), with cortical fibrils of sectioned graptolite periderm. Scale: 1 μ m.

It thus seems that at least some graptolites constructed their cortical periderm of collagen-like fibrils in association with polysaccharide substances of unknown composition. The thinner fibrils of the fusellar layer are also likely to have been collagenous although there are no definitive morphological characteristics to support this contention. No fibrous organic materials that have been studied from any extant organisms are known to us that compare as well morphologically and organizationally with graptolite periderm as do collagens. The presence of such a combination of protein and polysaccharide in the construction of the graptolite thecal wall would have provided not only considerable strength in the form of a composite material (see ref. 16), but also offered chemical insolubility and resistance to degradation by enzymes which may help to explain their fossil preservation.

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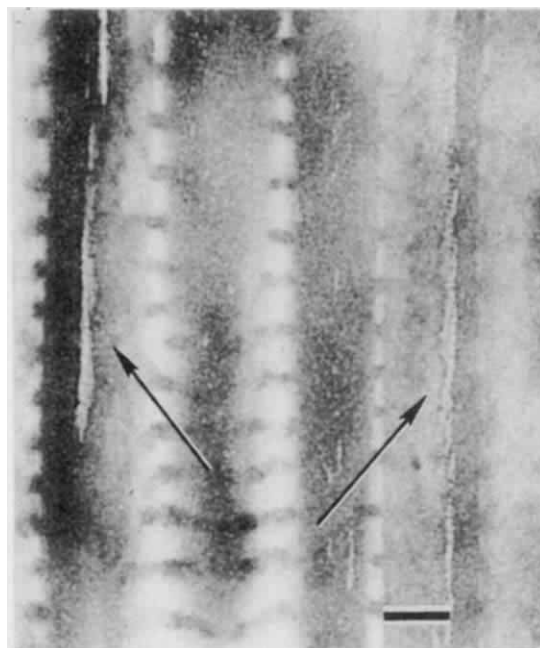


Fig. 4 Helical structures (arrows) in the central core region of cortical fibrils of *Dictyonema* sp. Scale: 0.1 μ m.

R. Kozłowski for material, A. Witmer for help with specimen preparation, D. Von Endt and P. E. Hare for the amino-acid analyses, and M. A. Jakus, K. A. Piez and B. Doyle for discussions. A. J. Bailey, K. A. Piez and R. Ross reviewed drafts of the manuscript.

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LETTERS TO NATURE

PHYSICAL SCIENCES

A 4.3 Aeon Pre-Imbrium Event

HERE we point out that published Rb-Sr data for Apollo 14 whole rock samples define an isochron age of 4.31 ± 0.04 aeon, which is interpreted as their time of igneous crystallization. Previously reported internal isochron ages of these rocks range from 3.87 to 3.96 aeon¹, in excellent agreement with their $^{40}\text{Ar}/^{39}\text{Ar}$ ages². We think that these approximate to the time of the Imbrium impact event and ejection of the material of the Fra Mauro Formation.

Much discussion of lunar basalt genesis is centred on Rb-Sr isotope systematics. In particular, it is often said that most whole rocks have model ages, relative to the initial $^{87}\text{Sr}/^{86}\text{Sr}$ ratio of basaltic achondrites (BABI=0.69898), of about 4.6 aeon. The best fit isochron to eleven mare-type basalts³⁻⁶ from Apollo 11 (Low-K), Apollo 12 and Apollo 15 is 4.56 ± 0.34 aeon, and the initial $^{87}\text{Sr}/^{86}\text{Sr}$ ratio is 0.69897 ± 10 . The whole rock isochron is statistically indistinguishable from that defined by the Apollo 14 whole rocks discussed here. If the internal isochrons relate to igneous crystallization of Apollo 11 and 12 magmas these observations may be explained in one of three ways.

(a) Variable contamination of magmas, derived from an Rb-depleted mantle, with Rb-enriched lunar crust generated 4.56 ± 0.34 aeon ago. This requires that essentially all Rb and radiogenic ^{87}Sr in the basalts is contributed by such a primordial crust. Support for this model has been adduced from correlation between supposed initial $^{87}\text{Sr}/^{86}\text{Sr}$ and the Rb content of the basalts, particularly in the case of the Apollo 14 lavas⁷.

(b) Formation of partial melts with Rb/Sr ratios essentially the same as their primordial source region. The range of measured Rb/Sr ratios in most mare-type basalts (0.003–0.01) may reflect corresponding inhomogeneities in the lunar mantle.

(c) Concentration of Rb and radiogenic ^{87}Sr in a mesostasis in the source region which enters the first-formed liquid. Subsolidus Sr-isotope homogenization does not occur and at each stage the liquid is removed from the system without equilibrating with the residual solids^{8,9}.

In all three cases, very little subsequent fractionation of the liquids can take place for the primordial Rb-Sr systematics to remain undisturbed, although in case (a) fractionation could occur before contamination.

Fig. 1 shows all Apollo 14 whole-rock Rb-Sr data published by the California Institute of Technology group plotted on a conventional isochron diagram. Previously only model ages relative to BABI have been reported for these data^{1,3}. Together with the analysis point for Apollo 15 sample 15415 (ref. 7), which is also probably pre-Imbrium material, the data define an isochron corresponding to an age of 4.31 ± 0.04 aeon. The initial $^{87}\text{Sr}/^{86}\text{Sr}$ ratio is 0.69905 ± 8 (both errors are 2 σ). Although the fit is less precise than those of the internal isochrons on these samples, only one of the whole-rock points (that for 14053) is more than 3 σ from the fitted line. The Rb-Sr isochron includes crystalline basalts, together with basaltic and other fragments and breccia matrix. The basalts are of both mare and non-mare types. The data for the breccia matrix samples are not essential to the isochron fit, but their collinearity indicates that they are derived from the same

source material as the basalts. The inclusion of sample 15415 does not affect the isochron age, but controls the precision with which the initial $^{87}\text{Sr}/^{86}\text{Sr}$ ratio is determined.

The age of 4.31 ± 0.04 aeon clearly records a single well defined lunar event. The simplest interpretation is that this event was the crystallization of a pre-Imbrium magma, or magmas, to form the parental material from which the Fra Mauro Formation was derived. The ages obtained from Rb-Sr internal isochrons and $^{40}\text{Ar}/^{39}\text{Ar}$ dating must relate to later stages in the evolution of these rocks. Papanastassiou and Wasserburg^{1,7} recognize two groups of Apollo 14 rocks with internal isochron ages of 3.88 ± 0.04 aeon and 3.95 ± 0.04 aeon and with quite different initial $^{87}\text{Sr}/^{86}\text{Sr}$ ratios. The isochron of Fig. 1, however, demonstrates closed-system increase of $^{87}\text{Sr}/^{86}\text{Sr}$ ratios for whole-rock samples from a common value at the time of their igneous differentiation 4.31 aeon ago. Thus the values of this ratio for individual rocks 3.9 aeon ago are dependent only on their Rb/Sr ratios and are of no petrogenetic significance. The distinction of two groups on the basis of age alone has not been statistically proven, and at present cannot be taken as evidence of two separate geological events. Textural and mineralogical evidence for post-crystallization events is variable: the breccias record a complex history of disruption and metamorphism, whereas some of the basaltic fragments appear to be simple igneous rocks.

We believe the following hypothesis, consistent with petrological observations, to be the simplest interpretation of Apollo 14 age data. A large scale igneous event 4.31 ± 0.04 aeon ago resulted in the production of basalts, anorthosites and more granitic rocks at or near the lunar surface in the Mare Imbrium region. Subsequently these rocks were brecciated and metamorphosed by a number of impact events, culminating in the creation of the Imbrium basin and ejection of the material of the Fra Mauro Formation. This last event was of sufficient intensity to cause local re-melting, according to model B or C, resulting in basaltic fragments such as sample 14310. This would also cause Ar-degassing and Sr isotope homogenization between minerals without disturbing the whole-rock systems, and is now recorded by the Rb-Sr internal isochrons and $^{40}\text{Ar}/^{39}\text{Ar}$ ages of 3.87–3.95 aeon. If the 70 m.y.

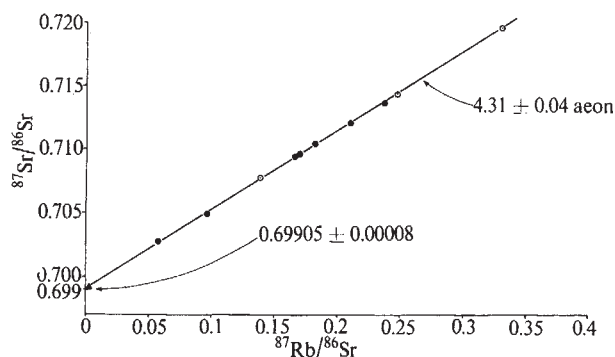


Fig. 1 Rb-Sr isochron diagram for all Apollo 14 whole-rock data published by the Lunar Asylum^{1,7}. Sample numbers from left to right are: 15415 A and B (Apollo 15); 14053; 14321, 191X-1; 14321, 144 "Light"; 14276A; 14276B; 14310; 14073; 14001, 7, 3; 14321, 144 "Dark"; 14001, 7, 1. Isochron fitted by the method of York¹³. ●, Basalts and basaltic classes; ○, other clasts and matrix; ▲, 15415 "Genesis rock".

interval between the two groups of mineral isochron ages is real, then an additional heating event, either before or after the impact, must have occurred.

The correlation of initial $^{87}\text{Sr}/^{86}\text{Sr}$ ratios with Rb content for Apollo 14 whole-rocks¹ was dependent on the erroneous assumption of 3.9 aeon for their time of igneous fractionation. As already pointed out, the whole-rock isochron with a single initial $^{87}\text{Sr}/^{86}\text{Sr}$ 4.31 aeon ago invalidates any petrogenetic interpretation of this variation, which is simply a consequence of radiogenic decay. Thus major support is withdrawn from the hypothesis that most of the lunar Rb was transferred to an acidic crust 4.6 aeon ago, at least in the Mare Imbrium region. Mixing with such a crust cannot explain the linear array of Fig. 1, nor does it seem likely that the fractionated Apollo 14 rocks were derived from an Rb-depleted lunar mantle. Because whole rock isochrons for Apollo 11 (low-K) and 12, on the one hand, and 14, on the other, are indistinguishable within the error it might be suggested that the primary lunar differentiation event, transferring most of the Rb to the crust, occurred 4.3 aeon ago rather than 4.6 aeon ago, and that contamination with this controls the Rb-Sr systematics of these rocks. The close fit of most soil samples, however, to a 4.6 aeon isochron^{1,3,14} is incompatible with this hypothesis.

The two mechanisms, which seem probable for the genesis of Apollo 14 rocks 4.3 aeon ago are, first, differing degrees of partial melting of source material which was or became isotopically homogeneous at the time, or second, extensive fractional crystallization of a single magma formed either with or without isotopic equilibration with its residuum. The initial $^{87}\text{Sr}/^{86}\text{Sr}$ ratio of 0.69905 ± 8 may be used to constrain the Rb/Sr ratio of the source region. Relative to BABI at 4.6 aeon the upper limit for this ratio would be about 0.015.

As the Rb-Sr whole-rock isochron records pre-Imbrium crystallization, loss of Rb by selective volatilization cannot have occurred during the Imbrium impact event.

Unlike the Apollo 14 basalts, the mare-type basalts fit an isochron which may be interpreted as the time of primary lunar differentiation rather than igneous crystallization. In view of the implications this may be best explained in terms of models B and C, both of which equally satisfy the Rb-Sr systematics. Positions on a 4.56 ± 0.34 aeon isochron are preserved due to the small amount of subsequent liquid fractionation with respect to Rb and Sr. The only exception is the relatively fractionated Apollo 11 high-K group which could well lie on a whole rock isochron similar in age to the internal isochrons (about 3.6 aeon), although their range of Rb/Sr ratios is too small to establish this. These rocks may have been generated by mechanisms similar to those advanced here for Apollo 14 non-mare type basalts. Furthermore, loss of Rb by volatilization^{11,12} cannot have occurred during fractionation of low-K Apollo 11 and Apollo 12 basalts. The general application of this process is clearly vitiated.

Our conclusions are therefore as follows: the crystallization event at 4.31 ± 0.04 aeon represents the earliest igneous activity on the Moon dated so far, and is evidence for the age of pre-Imbrium rocks. The Imbrium impact event is dated at approximately 3.9 aeon by Rb-Sr internal isochrons and $^{40}\text{Ar}/^{39}\text{Ar}$ ages of Apollo 14 rocks. We reject the control of the Rb-Sr systematics of lunar basalt whole rock samples by contamination with an Rb-enriched crust formed either 4.6 or 4.3 aeon ago and suggest that Apollo 14 magmas were formed either by differing degrees of partial melting with Sr-isotope equilibration throughout the source, or by extensive fractionation of a single magma. Alignment of 3.6 aeon Apollo 11 low-K and 3.2 aeon Apollo 12 basalts on a 4.56 ± 0.34 aeon through BABI records a primary differentiation event, although the age is statistically indistinguishable from that of crystallization of the Apollo 14 basalts. The preservation of this record through later melting events is explained by lack of significant liquid fractionation (with respect to Rb and Sr) following either Rayleigh melting, or else partial melting in

which the melt has the same Rb/Sr and $^{87}\text{Sr}/^{86}\text{Sr}$ ratio as the source.

This interpretation is mostly based on data obtained by the Lunatic Asylum of the California Institute of Technology. We thank Drs S. Moorbath, N. H. Gale, C. C. Schnetzler and S. W. Richardson for discussions.

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^{146}Sm : A Chronometer for p -Process Nucleosynthesis

UNTIL now, nucleosynthetic chronologies have been proposed only for r -process nuclei¹⁻⁵. Nucleosynthesis of the rare proton-rich isotopes is generally attributed to an as yet poorly understood p -process¹. We propose the use of the p -process radioisotope, ^{146}Sm ($\tau_{1/2} = 7 \times 10^7$ yr), as a possible nucleochronometer. The development of a p -process chronology would provide information about when the p -process occurred, which might provide a clue regarding the astrophysical site of the p -process.

Both the stable isotope, ^{144}Sm , and the radioactive, ^{146}Sm , are by-passed by s - and r -process nucleosynthesis; and thus form a pure p -process chronometric pair. The half life of ^{146}Sm allows its use as a determinator of the time between the end of p -process nucleosynthesis and the formation of solid bodies in the solar system. The formalism describing this chronology will be similar to those of ^{244}Pu and ^{129}I for r -process nucleosynthesis and would be referred to by Schramm and Wasserburg⁵ as a "short-lived" chronometer. We have estimated the relative p -process production of ^{146}Sm and propose a measurement which would enable it to become a nucleochronometer.

To develop a p -process chronology, it is necessary to estimate the relative production rates for the formation of p -process isotopes. Many workers^{1,6-15} have tried to elucidate the p -process mechanism. The primary mechanisms proposed have been (p, γ), (p, n) and (γ, n) reactions^{1,6,7,9,13,15}, absorption of positrons or photons^{11,12} and spallation reactions^{8,14}. All of these mechanisms have had a certain degree of success in explaining the abundances of some of the p -process elements, but do not solve the problem completely. The recent promising

calculations of Truran and Cameron¹⁵, based on (p,γ) and (γ,n) reaction rates, cannot be used directly to obtain a fit to the abundance of all the p -process nuclei. (The calculations differ from the observations by factors as large as 10^2 to 10^3 , in some cases.) This problem of predicting all the p -process abundances appears to be quite complex and for the present chronology problem we are mainly interested in predicting the p -process contribution to the formation of certain rare isotopes. Thus the Cameron¹⁶ p -process abundances (labelled "bypassed" in his Fig. 6) have been used to estimate the relative production (see Fig. 1).

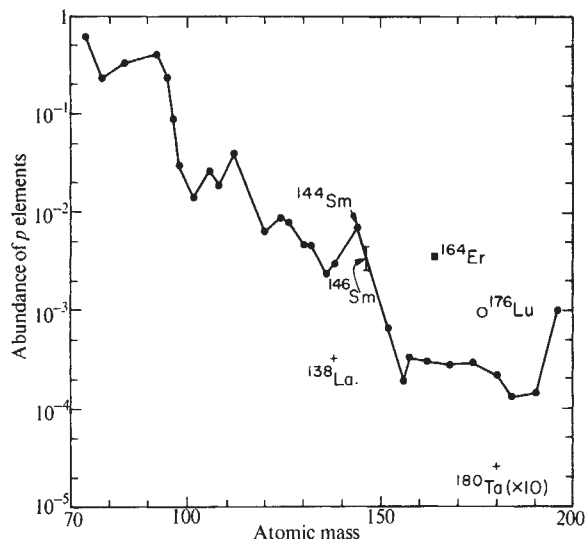


Fig. 1 Observed abundances of the p -process elements. The line connects the even Z , even N p -process nuclear abundances¹⁶. An estimate of the production of ^{146}Sm is made by interpolating between adjacent p -process abundances. Note that the odd Z , odd N nuclei, ^{138}La (abundance corrected to time of solar system formation) and ^{180}Ta are substantially below the even, even abundance curve. Note also that ^{176}Lu is above the even-even curve at $A=176$ even though the odd-odd p -process nuclei fall below the curve; this indicates that ^{176}Lu is not of p -process origin. It has also been found that no smooth semi-empirical curve which fits the other even, even p -process elements can be made to fit ^{164}Er . This isotope seems therefore to have an origin which is somewhat different from the other p -process elements¹² and has not been included on the even, even curve.

To see if there might be any peculiar behaviour in the p -process abundances near ^{146}Sm , various semi-empirical analyses were made, by least square fitting to the p -process abundances using various terms to account for intrinsic nuclear properties as well as possible production mechanisms. It appears from such analyses, that the atomic mass and shell structure of the p -process nuclei play a more important role in reproducing their abundances than the extrinsic terms based on the possible ways to form them from the r -process and s -process isotopes. It is interesting to note that there is only one p -process isotope, ^{164}Er , whose abundance cannot be fitted accurately by such a semi-empirical method [N_p (semi-empirical)/ N_p (obs.) ≈ 0.09]. Thus this isotope appears to have a peculiar history, which may be considered as a justification for the mechanism proposed by Reeves and Stewart¹⁰ and Arnould and Brihaye¹² in which the abundance of ^{164}Er is explained by photonuclear absorption processes.

It has been found that semi-empirical fits to the p -process abundances did not show any unusual behaviour in the region around ^{146}Sm . Thus the use of a smooth interpolation (see Fig. 1) of the observed abundances¹⁶ is justified for determining the relative production rate. Relative observed abundances in this mass region are accurately known since rare-earth elemental fractionation is small. From such an interpolation of the empirical p -process abundances the production rate

$P(146, 144)$ of ^{146}Sm relative to ^{144}Sm is found to be in the following range

$$0.35 \leq P(146, 144) \leq 0.6 \quad (1)$$

By using the Schramm and Wasserburg⁵ formalism, applicable to shorter lived isotopes, one obtains for the ^{146}Sm – ^{144}Sm pair

$$N(146, 144) = P(146, 144) \frac{\exp(-\lambda_{146}\Delta)}{\lambda_{146} T^*} \quad (2)$$

where $N(146, 144)$ represents the $^{146}\text{Sm}/^{144}\text{Sm}$ ratio at the time of solidification of objects in the solar system, λ_{146} is the decay constant for ^{146}Sm and Δ is the time interval between the last p -process nucleosynthetic event contributing to the solar system abundances and the time of solidification of objects in the solar system. By using the r -process isotopes, Schramm and Wasserburg⁵ have determined a range for Δ of $7.5 \times 10^7 \leq \Delta \leq 2.5 \times 10^8$ yr with a best estimate of 10^8 yr. The parameter T^* represents the degree to which the rate of the last nucleosynthetic events contributing to the solar system abundances differs from the mean rate of nucleosynthesis. A value of $T^* \sim 5 \times 10^9$ yr corresponds to continuous uniform nucleosynthesis whereas smaller values of T^* correspond to chronologies of nucleosynthesis which are spiked near the time of separation of the solar system. A current best estimate for T^* from the r -process chronologies ^{127}I – ^{129}I and ^{244}Pu – ^{232}Th is a nearly uniform value for T^* of $\sim 10^9$ yr. Using these r -process values for Δ and T^* with $\lambda_{146} = 10^{-8} \text{ yr}^{-1}$ and $P(146, 144) = 0.5$ we obtain a rough estimate for $N(146, 144) \approx 0.02$. It must be remembered at this point that the values of Δ and T^* for the p -process may be very different from those based on the r -process isotopes. The value of $N(146, 144)$ obtained here is quoted only to check the feasibility of possible experiments which must be done to develop the p -process nucleochronology.

With a 10^8 yr lifetime the ^{146}Sm present at the time of solidification would no longer be available for observation at the present time 4.6×10^9 yr later. ^{146}Sm does, however, alpha decay to ^{142}Nd . Therefore the isotopic composition of Nd should vary with the amount of Sm with which it was in contact at solidification. That is, the amount of cosmogenic ^{142}Nd is proportional to the Sm/Nd elemental ratio in a sample. Thus the way to determine the parameters of the p -process nucleochronology is to look for ^{142}Nd anomalies in meteorites.

This type of experiment is feasible since the Sm/Nd ratio can vary by a factor as large as 2 to 6 from meteorite to meteorite¹⁷, and this ratio can vary by a factor as large as 10^3 due to chemical fractionation in minerals^{17,18}. Hasking *et al.*¹⁹ have found Nd/Sm = 1.4 in the olivine phase of the pallasite Brenham and Nd/Sm = 5.5 in the olivine phase of the pallasite Thiel Mountain. The ratio $N(146, 144) \sim 0.02$ would lead to isotopic variations, δ , in $^{142}\text{Nd} \approx 1.1 \times 10^{-3}$ since

$$\delta = \left(\frac{^{146}\text{Sm}}{^{142}\text{Nd}} \right) = \frac{^{146}\text{Sm}}{^{144}\text{Sm}} \times \frac{^{144}\text{Sm}}{\text{Sm}} \times \frac{\text{Nd}}{^{142}\text{Nd}} \times \left[\left(\frac{\text{Sm}}{\text{Nd}} \right)_1 - \left(\frac{\text{Sm}}{\text{Nd}} \right)_2 \right] \quad (3)$$

where 1 and 2 represent the olivine phases of the two pallasites,

$$\frac{^{144}\text{Sm}}{\text{Sm}} = 3 \times 10^{-2}$$

and

$$\frac{^{142}\text{Nd}}{\text{Nd}} = 0.27$$

An effect of $\sim 10^{-3}$ in the ^{142}Nd meteoritic composition is detectable with the new improved mass spectrometry techniques²⁰ which have been able to measure isotopic compositions in other rare-earth elements²¹ to 1 part in 10^4 . In

Table 1, the expected variations in ^{142}Nd are listed for the range of Δ , T^* and $P(146, 144)$ given above. If in addition to fractionation from meteorite to meteorite the possibility of mineral fractionation is included, it may be possible to have a fractionation of Sm/Nd by factors of the order of 100 or more. For minerals with Sm/Nd varying from 0.026 to 4.87 (see ref. 17), one would expect ^{142}Nd isotopic anomalies of $\approx 10^{-2}$ (for the above choice of parameters). Preliminary work on Nd isotopic anomalies is now being carried out by Kohman and Karol²². This type of measurement would offer vital information on the chronology of the p -process. Since ^{146}Sm is a short-lived isotope, information is obtained mainly on the few hundred million years preceding the time of solidification of the solar bodies. In particular one expects from the proposed experiments that the current hypothesis in which the time of the p -process is correlated with the time of the r -process could be critically examined.

Table 1 Expected Variations in the Abundance of ^{142}Nd

Δ (yr) T^* (yr)	2.4×10^8		10^8	
	$P(146, 144)$ =0.35	$P(146, 144)$ =0.6	$P(146, 144)$ =0.35	$P(146, 144)$ =0.6
5×10^9	3.4×10^{-5}	5.8×10^{-5}	1.5×10^{-4}	2.6×10^{-4}
10^9	1.7×10^{-4}	2.9×10^{-4}	7.6×10^{-4}	1.3×10^{-3}
10^8	1.7×10^{-3}	2.9×10^{-3}	7.6×10^{-3}	1.3×10^{-2}

If ^{146}Sm yields values for Δ and T^* consistent with those obtained by r -process chronometers, then this would imply that the last contributions to the solar system from p -process and r -process nucleosynthesis occurred at the same time. If, however, the values of Δ and T^* from ^{146}Sm differ significantly from those of the r -process, this would imply processes separated in time. The usual assumption is that Δ represents the time interval between the separation of the solar system gas from the interstellar gas and the time of solidification. If Δ from ^{146}Sm differs from the Δ of the r -process, then the assumption that the interstellar gas is well mixed with respect to the various nucleosynthetic processes would have to be questioned.

To summarize, we have found that information on the formation of the radioisotope, ^{146}Sm , can be used as a good chronometer for the p -process and give some clues on its history if a crucial experiment can be carried out; namely a mass spectrometric determination of ^{142}Nd anomalies in samples with solidification ages $\sim 4.6 \times 10^9$ yr.

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Pulsating X-ray Sources

It has been natural to suggest that the several pulsating X-ray sources¹⁻⁵ with periods ~ 1 s are associated with matter at high densities and in particular with white dwarfs, neutron stars or black holes. But pulsars are primarily radio sources and no radio pulsations have been observed from these objects. Further, the timing of the pulses does not appear to have the essential constancy of that of the pulsars. This suggests that rotation is not the most likely explanation of the pulsations. But neutron stars have periods of oscillation which are too short, and it is difficult to explain the short period X-ray sources in terms of oscillating white dwarfs. Here I suggest that these X-ray sources are stars with central densities intermediate to those of neutron stars and white dwarfs.

It is generally believed that stable white dwarfs have central densities $\rho_c \lesssim 10^{11} \text{ g cm}^{-3}$, and that stable neutron stars have $\rho_c > \rho_m$ (where $\rho_m \approx 10^{14} \text{ g cm}^{-3}$) is the central density for which the mass is a minimum. Recent investigations⁶ of the stability of neutron stars have indicated that dynamically stable neutron stars (that is, stable against small adiabatic radial perturbations) with central densities in the region $\rho_1 < \rho_c < \rho_m$ (where $\rho_1 \approx 8 \times 10^{12} \text{ g cm}^{-3}$) can also exist. But it has been suggested^{7,8} that these stars are unstable over long time scales. I have carried out more rigorous investigation of this problem⁹, under the simplifying assumptions that the linear approximation is good and that the nuclear relaxation times t_n are constants. That work shows that these stars are unstable over long time scales. It seems plausible that the time scale of the instability⁷ is of the order of the nuclear relaxation times t_n . Crude estimates⁷ indicate that $100 \text{ day} \lesssim t_n < \infty$. But the t_n are strongly amplitude (δr) dependent. For example, the modified Urca ($n=u$) reactions have $t_u \propto (\delta r/r)^{-6}$ so for $\delta r/r \sim 0.1$, $t_u \sim 100 \text{ day}$; but if $\delta r/r \sim 0.01$, $t_u \sim 10^6 \text{ yr}$. For small oscillations, therefore, the star could exist long enough to be of astronomical interest. In addition, the presence of a superfluid energy gap would tend to suppress the reactions and hence lengthen the relaxation times.

Because of the complicated dependence of t_n on amplitude⁷, and of the adiabatic index⁷⁻⁹ on t_n , the stability problem is highly non-linear. No analysis of the stability of these stars including non-linear effects has been carried out, so there is no evidence that, if these stars can be formed, they could not exist for a sufficiently long time (say $\sim 10^4 \text{ yr}$) to be of astronomical interest. The slow collapse of the star provides an adequate energy source for the X-ray luminosity. Mass accretion is another possible energy source.

The masses of these stars^{6,10} are $\approx 0.7 M_\odot$ and their radii $\lesssim 10^8 \text{ cm}$. Because they are weakly bound it is unlikely that their formation would be accompanied by that of a supernova remnant. An important feature⁴ of the X-ray sources is that no supernova remnants have been associated with them. The pulsation frequency spectrum of these stars is complicated and probably time varying, with an apparent⁶ fundamental

period of ~ 1 s over a wide range of ρ_c , the period going to infinity over a narrow range of ρ_c near the instability point at $\rho_c = \rho_1$. The presence of multiple periods³ suggests that in addition to the fundamental mode higher modes are also excited.

I therefore suggest that some of the pulsating X-ray sources are vibrating stars of densities intermediate between those of white dwarfs and neutron stars, and are probably undergoing slow collapse eventually to become neutron stars or black holes.

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Seismic Anisotropy in the Lower Oceanic Crust

Hess¹ suggested that upper mantle compressional wave velocities near the Mendocino and Molokai fracture zones of the Pacific vary with azimuth and this anisotropy is the result of preferred mineral orientation. Recent seismic refraction evidence indicates that in many regions the Earth's upper mantle is anisotropic²⁻⁴ and the observed anisotropy in the upper mantle correlates well with laboratory studies of velocity anisotropy in dunites and peridotites^{5,6}. Although anisotropy complicates seismic refraction investigations its importance cannot be overestimated; it places severe limitations on probable upper mantle compositions and provides a means of estimating the stress fields which existed during the formation of preferred mineral orientation in the upper mantle.

Laboratory studies of seismic velocities in rocks^{7,8} show that many common crustal rocks are highly anisotropic to compressional wave propagation, so it is plausible that in many regions the Earth's crust is anisotropic, and Dorman⁹ has recently presented seismic data which indicate anisotropy of the continental crust in the south-eastern United States. Here I report evidence for seismic anisotropy in the lower oceanic crust, which is interpreted as due to preferred orientation of amphibole.

The lower oceanic crust has been frequently referred to as being rather uniform in seismic velocity. This is certainly the case when its velocities are compared with those of the overlying layer 2 of the oceanic crust. But a plot of lower oceanic crustal velocities tabulated by Raitt¹⁰ shows considerable variation (Fig. 1). Three recent seismic investigations of the oceanic

crust suggest strongly that some of the variation may result from anisotropy.

Keen and Barrett⁴, in their study of mantle seismic anisotropy of the Pacific Ocean basin off the coast of British Columbia, report oceanic crustal velocities for two reversed profiles, one in a north-south direction and the other in an east-west direction. The shot lines crossed one another at approximately 134° W and 51° 30' N. The crustal structure determined by Keen and Barrett gives a layer 3 velocity of 6.99 km s⁻¹ for the north-south profile and a velocity of 6.73 km s⁻¹ in an east-west direction. A circular pattern of shots was established around these profiles to obtain upper mantle first arrivals. Keen and Barrett found 8% anisotropy in the upper mantle, but made no mention of the possible anisotropy of the lower crust in this region. Their data indicate that the low velocity in layer 3 is nearly parallel to the fast velocity in the upper mantle, which approximates the direction of seafloor spreading in this region.

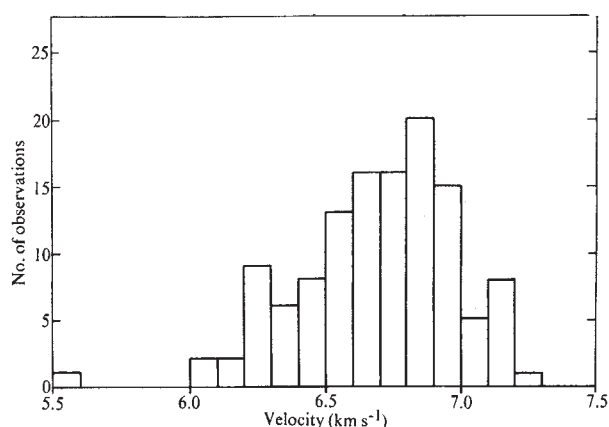


Fig. 1 Variations in layer 3 velocities (after Raitt¹⁰).

Seismic refraction studies along the Hawaiian Ridge¹¹ also suggest the presence of seismic anisotropy in the lower oceanic crust. In this study several refraction lines were run approximately normal to one another in order to investigate upper mantle anisotropy. The pertinent refraction traverses are those flanking the ridge crest approximately parallel (Y, Z) and normal (B, E, F, N, X) to the trend of the ridge. The lower crustal velocities parallel to the ridge are fast (6.9 to 7.1 km s⁻¹), whereas velocities normal to these traverses tend to be relatively slow (6.3 to 6.7 km s⁻¹).

Seismic refraction profiles of young oceanic crust in the Scotia Sea of the South Atlantic Ocean¹² suggest that layer 3 may be highly anisotropic in this region. Profiles 83 and 84, which are approximately normal to each other in the West Scotia basin, have layer 3 velocities of 6.29 and 6.75 km s⁻¹. Profiles 101 and 102, located on the South Georgia platform, are also perpendicular but unreversed, and have lower crustal velocities of 6.95 and 6.18 km s⁻¹. For both sets of stations the slow velocities are north-south. Ewing *et al.*¹² noted the discrepancy in velocities given in profiles 101 and 102 and suggested that they are apparent velocities produced by a dipping layer.

It is difficult to attribute the wide range in velocities of layer 3 in these regions to observational error. Rather, it seems likely that these observations are related to seismic anisotropy in the lower oceanic crust. Detailed seismic investigations of crustal anisotropy will be necessary to establish how common anisotropy is in the lower crust and the exact nature of this anisotropy.

Recent studies of elastic wave propagation in rocks suggest a probable cause of oceanic crustal seismic anisotropy. Common igneous rocks are nearly isotropic⁷, so lower crustal

regions which contain abundant gabbro would be expected to show little variation of compressional wave velocity with azimuth. Metamorphic rocks are highly anisotropic^{7,8}, and in particular, hornblende bearing metamorphic rocks such as amphibolites have velocities similar to those observed for layer 3, combined with a strong preferred mineral orientation which produces high seismic anisotropy. Christensen⁸ found maximum compressional wave velocities at 1 kbar of 7.21 and 6.97 km s⁻¹ for propagation parallel to maximum concentrations of hornblende *c* axes in two amphibolites. Further, the hornblende *c* and *b* axes show a strong tendency to lie in the foliation planes of the amphibolites. Propagation normal to the foliation planes gave minimum velocities at 1 kbar of 6.29 and 6.01 km s⁻¹. If the crustal anisotropy cited here does arise from preferred hornblende orientation, it seems that in the Hawaiian and Scotia Sea regions the amphibolite foliation planes are dipping steeply and the hornblende *c*-axes maxima are nearly horizontal and parallel to the fast velocities. If the two profiles off British Columbia give maximum anisotropy, the lower anisotropy in this region would be consistent with a nearly horizontal foliation plane.

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Upper Atmosphere Zonal Winds

ANALYSIS of the changes in inclination of Earth satellite orbits has indicated¹ that the average rotation rate of the upper atmosphere increases from about 1.1 revolutions day⁻¹ at 200 km to about 1.4 revolutions day⁻¹ at 350 km, and then decreases to about 0.8 revolutions day⁻¹ at 500 km. These values represent averages over all local times. Recently, however, with the aid of accurate observations from the Hewitt cameras at Malvern and Edinburgh, it has become possible to determine upper atmosphere zonal winds over shorter intervals of local time—between 4 and 8 h, rather than 24 h.

Analyses of the Cosmos 268 rocket (1969–20B) and the Cosmos 307 rocket (1969–94B) have both indicated^{2,3} that the zonal winds at heights of 230 to 250 km are strongest from west to east during the night, between 2100 and 0300 local time, when typical velocities are 100 to 150 m s⁻¹. They are less strong from east to west in the daytime, typical velocities being 50 to 100 m s⁻¹. These results confirm previous indications from orbital analysis⁴ of strong west-to-east evening winds and are in good accord with existing results from

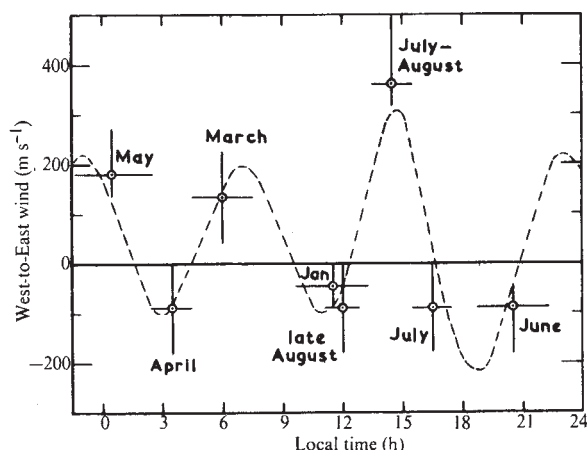


Fig. 1 Zonal winds at heights of 150–170 km in 1970, obtained from analysis of the orbit of Cosmos 316.

measurements of the motion of vapour trails from sounding rockets at heights above 220 km. West-to-east winds in the evening have been reported at latitudes 30° to 40°, of magnitude 110 m s⁻¹ (ref. 5), 100 m s⁻¹ (ref. 6) and 110 m s⁻¹ (ref. 7) at heights of 240 km, 200 to 260 km and 275 km respectively. A recent review⁸ of 12 vapour trail measurements above 220 km indicates a mean west-to-east wind in the evening of about 80 m s⁻¹, and a mean east-to-west wind near dawn of 20 m s⁻¹. The good agreement between results using these different techniques seems enough to confirm the general hypothesis that the zonal winds at heights of 220 to 250 km are from west to east and approximately 100 m s⁻¹ in magnitude in the late evening, and from east to west, but weaker, in the morning.

Analysis⁹ of the orbit of Cosmos 316 (1969–108A) has, however, revealed a quite different pattern at heights near 160 km. The simple distinction between day and night no longer applies, and the situation is much more complex. Fig. 1 shows the zonal wind speeds deduced from the analysis of the orbit of Cosmos 316, plotted against local time. The vertical bars indicate the estimated errors (1σ) above and below the values determined; the horizontal bars indicate the spread in local time (two-thirds of the variation in local time at perigee, plus 1 h); and the month to which the observations apply is indicated beside the points. These dates cover the complete life of the satellite from January to August 1970. The variations may possibly be linked with height, latitude or date rather than local time: but the height range is fairly small, varying between 150 and 170 km (with one value at 135 km); and most of the results can be regarded as averages over latitudes between 25° N and 25° S. During the satellite's life the local time at perigee moved through only 26 h, and consequently there is no overlap which could confirm or refute the assumption of a variation with local time. The results are clearly consistent with an 8-h oscillation, as indicated by the broken line; equally clearly, the results are inadequate in number to establish that this oscillation is real.

A change in the pattern of wind speeds when the height changes from 240 km to 160 km is to be expected: measurements of wind speeds from the motion of vapour trails reveal considerable variations in wind direction, with the wind velocity vector usually rotating anti-clockwise viewed from above, as height increases up to about 160 km. As height increases above 160 km, the wind usually remains more constant in direction^{5,8,10}.

Measurements of vapour trails are more numerous at heights near 160 km than at heights above 200 km, but the greater number of results serves chiefly to confuse the picture rather than clarify it. No pattern has yet been established; if there is a pattern, it probably depends on latitude and season as well as local time, and may also possibly be affected by solar activity and longitude. A review by Rosenberg¹¹ indicates

east-to-west winds of order 50 m s^{-1} in mid latitudes at 160 km height in the dawn twilight during spring, summer and autumn, that is, at about 0400–0500 local time: this is consistent with Fig. 1. The only other contours given by Rosenberg for a height of 160 km apply at evening twilight during spring–summer, that is, at about 2000 local time, and give east-to-west winds of 30 m s^{-1} , again consistent with Fig. 1. In spite of this partial agreement, Rosenberg's contours indicate that the winds at heights up to about 160 km are everywhere less than 70 m s^{-1} , and this is not consistent with Fig. 1.

The possible 8-h oscillation in Fig. 1 raises the question of a third-harmonic tide. Woodrum, Justus and Roper¹² have analysed 42 vapour-trail wind measurements at heights between 95 and 135 km to obtain 24, 12 and 8-h components. Of the three, the 8-h component is the most uncertain, but it exhibits more energy than the other two modes at heights above 120 km. So the idea of an 8-h tidal oscillation at 160 km should not be ruled out, and may be worth bearing in mind in future studies. But I emphasize that Fig. 1 in itself is completely inadequate to justify such a hypothesis: in a situation so complex, with the potential controlling parameters so numerous, it is quite possible that seasonal and latitude effects have combined to give a spurious impression of dependence on local time.

One further feature of Fig. 1 calls for comment, namely the west-to-east wind of over 300 m s^{-1} near 1500 local time. This wind seems so strong as to be rather unlikely, but it cannot be spirited away without doing violence to the data. The measurement applies in the southern hemisphere, between July 24 and August 20, 1970 (or possibly only between July 24 and August 7) at a height near 150 km and at latitudes 0° – 25° S. There are three phenomena that may contribute towards this unusual wind. First, the semi-annual minimum of air density occurred early in August, the density at 150 km height being 30% lower¹³ than at the maximum in April 1970. Second, the wind models up to a height of 130 km derived by Groves¹⁴ show that the mean daily wind at 130 km height and latitude 20° S has its maximum west-to-east velocity (35 m s^{-1}) in July–August (its maximum east-to-west velocity of 14 m s^{-1} is in February). The value of 35 m s^{-1} , although of course much lower than 300 m s^{-1} , is an average over the complete 24 h. Third, and perhaps most important, July 1970 was the most disturbed month geomagnetically of the 1968–70 sunspot maximum, the geomagnetic index Ap having a mean value of 25 between July 21 and July 31; and there were 3 strong geomagnetic storms between July 9 and August 20, with maxima in Ap of 87, 92 and 115. Such geomagnetic disturbances are known to be associated with very strong winds (up to 500 m s^{-1}) in the auroral zones¹⁵ and these may propagate to lower latitudes¹⁶. Nevertheless, none of these three effects seems likely to be capable of generating west-to-east winds of order 300 m s^{-1} persisting for about two weeks, or correspondingly stronger shorter-lived winds, so the high wind speed remains somewhat anomalous.

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Atmospheric Dimethyl Sulphide and the Natural Sulphur Cycle

ALL models of natural processes for the transfer of sulphur on a global scale^{1–4} require some volatile or gaseous sulphur compound to complete the cycle by providing a vehicle for the transfer of sulphur from the sea through the air to the land surfaces. In the past, this role has been assigned to H_2S and an average atmospheric concentration of 2×10^{-10} by volume satisfied the mass transfer needs of the models. Attempts to detect the presence of these concentrations of H_2S have always failed and, more important, the ocean surface waters are much too oxidizing to permit the existence of H_2S at concentrations sufficient to sustain an atmospheric equilibrium concentration of 2×10^{-10} by volume. Many elements form volatile methyl derivatives; Challenger⁵ reported that many living systems produced dimethyl sulphide (DMS), and that prominent among them were marine algae. Here we suggest that DMS is the natural sulphur compound which fills the role originally assigned to H_2S ; that of transferring sulphur from the seas through the air to land surfaces.

We have made preliminary measurements of the concentration of DMS in seawater, and of its emission by land plants, soils and marine algae. Analyses were made by gas chromatography using a flame photometric detector specific for sulphur compounds. The experimental details will be published elsewhere. A brief summary of the experimental results is listed in Table 1.

The seawater samples were taken at sites along the southern coast of England in December, January and February 1971–1972 and during the voyage of the RRS Shackleton between Montevideo and the UK in March 1972. All samples taken showed the presence of DMS and the average seawater concentration was $1.2 \times 10^{-11} \text{ g ml}^{-1}$. The distribution coefficient of DMS between air and seawater was found to be 0.30, corresponding to an atmospheric concentration of 1.2 p.p.b. at equilibrium. So far we have failed to find DMS in samples of the open air, collected by cryogenic trapping, although this is not surprising since oxidants simultaneously collected could have destroyed DMS before analysis.

The emission of DMS from a few samples of marine algae, mostly varieties of *Laminaria*, ranged from 50 – $400 \times 10^{-12} \text{ g}$

Table 1

Source	No. of measurements	Emission rate $10^{-12} \text{ g g}^{-1} \text{ h}^{-1}$ ($\pm$ s.d.)	Concentration $10^{-11} \text{ g ml}^{-1}$ ($\pm$ s.d.)
Soils			
Washington, DC	6	47 (26)	
Walnut Creek, CA	11	54 (31)	
Seattle, WA	5	32 (20)	
Baton Rouge, LA	8	66 (42)	
Lewiston, ID	15	84 (51)	
Pullman, WA	7	21 (14)	
Seawater			
Atlantic Ocean	23		1.2 (2.7)

BIOLOGICAL SCIENCES

Possible Role of Repeated Nucleotide Sequences in DNA in the Evolution of Life Spans of Differentiated Cells

THE life span of cells from tissues which do not regenerate can vary by a factor of forty to fifty between species for a given tissue. It seems probable that this is a function of different rates of the same molecular processes rather than of qualitative differences in the ageing process in cells of different species.

Few¹⁻⁵ of the many theories on the molecular basis of ageing consider rate of change and mechanism of change separately. Various explanations for the species differences have been put forward: a relationship has been suggested between the rate of somatic mutation and the rate of ageing; or between the phylogenetic "load" of deteriorative mutations and life span; a genetic "programme of ageing" has been proposed, as well as changes in the expression of certain genes—"generators of molecular errors"—and a genetic control mechanism governing the rate of repair. I suggest a new approach to the problem which makes it possible to explain the different rates of ageing even assuming that the rate of mutation, errors of replication and other molecular accidents are equal per molecule of DNA or diploid genome.

It has been shown⁶ that in the genome of any higher organism the DNA of chromosomes is represented by two groups of nucleotide sequences: unique and repeated (from several to a million times). The ratio of unique to repetitious DNA varies between species. It is known that the ratio of transcription of repeated and unique cistrons changes during morphogenesis and is tissue specific^{7,8}, but there is no direct evidence that this is connected with the tissue specificity of the DNA^{9,10}. Nor is there any evidence that molecular ageing is related to changes of nongenetic "metabolic" DNA copies¹⁰ or selective repression with age of repetitious DNA sequences¹¹. I suggest that one possible function of repetition in DNA sequences is to prevent accumulation with time of coded information from molecular accidents. If the concomitant increase in phenotypic expression of the repeated gene is deteriorative for metabolism it can be compensated by a reduction in speed of transcription, shortening of the life span of RNAs transcribed from repetitious DNA, a selective decrease in the amount of repeated RNA released from the nucleus, or regulation at the level of translation.

Molecular hybridization experiments indicate that rRNA and tRNA genes are repetitious in all species^{6,12}: the genomes of eukaryotes have from 100 to 500 genes for the principal rRNA and from 800 to 1,300 genes for sixty to 100 different tRNAs. The principal rRNA gene is, therefore, repeated ten to twenty times more often than those of the different tRNAs. Thus in a given period of time random mutations can induce more functionally expressible changes in the tRNA portion of the genome than in the rRNA portion, and this probably explains the evolutionary stability of rRNAs in contrast with the greater inter-species variation of the tRNAs. Changes in tRNA genes may also be more important for functional changes during ageing¹³.

This leads to the conclusion that, all other conditions being equal, genomes with a relatively large number of repetitious vital genes will be associated with a longer life span in differentiated cells. The correlation is not direct, however, because of differences in the importance of the different genes and because some repetitious sequences do not carry genetic information at all. The hypothesis of a protective function for repetition can also explain tissue specific differences in ageing rate, because of the different representation of unique (sensitive) and repeated (protected) sequences in the genetic sub-programmes of differentiated cells. This does not apply to regenerating tissues, in which the life span of the individual cells is not a limiting factor. Repetition in living structures in general enhances survival,

$\text{g}^{-1} \text{h}^{-1}$ of fresh wet tissue. These were wintertime measurements and Challenger's experiments⁴ would suggest that other species of algae at other seasons are more prolific in their output.

The emission of DMS from living intact leaves of oak, cotton, spruce and pine trees ranged from 2 to $43 \times 10^{-12} \text{ g g}^{-1}$ of oven-dried tissue per hour; the rate of emission for decaying leaves from the same species was 10 to 100 times greater. Whether the metabolism of the leaf is directly responsible for this emission of DMS, or whether it is a secondary result from the microbial populations living on the surface of the leaves, is unknown.

Soil samples were collected in various places in the United States in December and January 1971-1972. All soils produced DMS if contained in flasks sealed with glass wool, allowing restricted exchange of gases with the surrounding air (Table 1). If the flasks were completely sealed DMS production fell and hydrogen sulphide was produced. The oxygen content of the sealed flasks fell by $<1\%$, thus showing that anaerobic conditions were not responsible for H_2S synthesis. The CO_2 concentrations in the sealed flasks increased to several thousand parts per million. Possibly either the high CO_2 concentrations suppressed the microorganisms synthesizing DMS and/or stimulated microorganisms producing H_2S .

From these experiments which confirm Challenger's work it would seem that DMS is ubiquitous in the biosphere. The quantity of sulphur of biological origin required to balance the sulphur cycle by transfer through the atmosphere is approximately $10^8 \text{ tons yr}^{-1}$ (ref. 4). If we assume that this travels mostly as dimethyl sulphide and that it has an atmospheric residence time of one week, characteristic of a moderately reactive gas, then the anticipated equilibrium concentration would be 4×10^{-10} parts by volume. The seawater concentrations and the emissions from soil and plants, if they are representative, could sustain an atmospheric concentration of this order. We therefore think that DMS may be considered as the candidate compound in the natural transfer of sulphur of biological origin.

If this role for DMS is correct it raises some interesting possibilities concerning its fate in the atmosphere. It has been shown⁶ that the oxidation of DMS under conditions simulating atmospheric photochemical oxidation, albeit at much higher concentrations, leads principally to dimethyl sulphoxide, methane sulphonc acid, sulphur dioxide and sulphuric acid. Dimethyl sulphoxide will be an early product of oxidation and because of its low volatility and hygroscopic nature would presumably be scavenged from the air by rain or surface adsorption. DMS may therefore be a lesser potential source of sulphate aerosol than are the inorganic sulphur compounds which enter the atmosphere. Methane sulphonc acid, however, has physical properties closely resembling sulphuric acid and would, like the latter substance, have a long atmospheric lifetime as an aerosol of the free acid or its ammonium salt.

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and repetition at the level of the gene is no exception, particularly where it affects vital genes. But there are, of course, many influences on the rate of ageing of cells.

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Biosynthesis of Mescaline and N-Acetylmescaline by Mammalian Liver

We have shown that mescaline, a well established hallucinogen found in the peyote cactus, can also be formed by mammalian liver from an appropriate precursor. An enzyme can be extracted from various mammalian tissues (by centrifugation at 100,000g for 1 h), including human brain and liver that transfers a methyl group from S-adenosyl[Me-¹⁴C]methionine (¹⁴C-SAM) to 4-O-methylated catecholamine metabolites to form corresponding 3,4-di-O-methylated compounds^{1,2}. One of the substrates for this enzyme is iso-N-acetylmethoxytyramine (i-NAMT), which is converted to N-acetyl-3,4-dimethoxy-β-phenethylamine (NADMPEA). An enzyme in the same fraction of liver can transform 4-hydroxy-3,5-dimethoxy-β-phenethylamine (4-desmethylnescalinine or 4-DMM) to mescaline (3,4,5-trimethoxy-β-phenethylamine), and N-acetyl-4-hydroxy-3,5-dimethoxyphenethylamine (N-acetyl-4-desmethylnescalinine or NA-4-DMM) to N-acetylmescaline.

The supernatant fraction of rat liver obtained after centrifugation at 100,000g for 1 h (pH 9.0, 0.1 M Tris-HCl buffer) was used with incubation conditions as described in Table 1. Blanks consisted of samples less substrate, or with protein modified by heating. Reactions were terminated by the addition of 0.2 ml. of 3 N HCl for acidic and neutral metabolites and 0.2 ml. of 1 N NaOH for basic metabolites. The sample was extracted once with 6 ml. of toluene and isoamyl alcohol, 90 : 10 (v/v). The extract was evaporated to dryness with nitrogen and the residue redissolved in methanol with the appropriate reference compound, chromatographed on silica gel fibreglass strips (Gelman Instrument Co.) in benzene, heptane and diethylamine 10 : 5 : 1, and the radioactivity in the appropriate area was determined by liquid scintillation spectroscopy. The recovery of both products was better than 80%.

Table 1 shows that in the presence of substrate a radioactive product was formed which was extractable into the solvent and recovered after chromatography. When substrates were omitted, only a small amount of radioactivity was recovered. These results indicate that there is an enzyme present which catalyses the transfer of a ¹⁴C-methyl group in significant amounts from ¹⁴C-SAM to each of the substrates.

The radioactive product, presumably mescaline, formed after incubation of 4-DMM was further identified by chromato-

graphy in four solvent systems, by co-crystallization to constant specific activity and by derivatization to N-acetylmescaline, 2,6-dibromo-N-acetylmescaline and trimethoxybenzoic acid, which were further recrystallized without loss of molar specific activity. The radioactive product derived from incubations of NA-4-DMM was characterized by similar methods.

When the supernatant fraction was used in incubations with 4-DMM or NA-4-DMM, maximal activity was obtained at about pH 9 in the presence of Mg²⁺. Biosynthesis of the mescalines is strongly inhibited by 10⁻³ M EDTA, and activity can be restored by the inclusion of 10⁻¹ M MgCl₂ in an incubate containing 10⁻³ M EDTA (Table 1). The K_m against NA-4-DMM is around 10⁻⁴ M. The K_m against SAM (10⁻³ M NA-4-DMM) is about 10⁻⁵ M. The reaction maintains good linearity through a ten-fold range of protein concentrations for both 4-DMM and NA-4-DMM. These properties are similar to those for the enzyme involved in the formation of di-O-methylated catecholamine metabolites except that the K_m against i-NAMT is 6.9 × 10⁻⁴ M. The mescaline-forming enzyme is most active against substrates carrying the hydroxy substituent in the 4 position. There was relatively little activity against 3-DMM. In contrast, in the formation of dimethoxy compounds, the enzyme preferentially transfers a methyl group to the 3 position (our unpublished results). The presence of both a 3 and a 5-methoxy substituent on the favoured mescaline precursor may have a strong directional effect on the O-methylating enzyme, which overcomes expected steric hindrance toward methylation of the 4 hydroxy group. Alternatively, mescaline and N-acetyl-

Table 1 Rates of Formation of Mescaline and N-Acetylmescaline in Various Conditions

System	Substrate (M)	Product formed * (d.p.m./mg super. protein/h)	
		Mescaline (from 4-DMM)	N-Acetyl- mescaline (from NA-4-DMM)
I, Rat liver			
Boiled protein	1 × 10 ⁻³	200	185
No substrate	0	325	280
Complete	1 × 10 ⁻⁴	19,000	40,000
Complete	2 × 10 ⁻⁴	—	57,500
Complete	3 × 10 ⁻⁴	—	61,500
Complete	5 × 10 ⁻⁴	—	70,100
Complete	1 × 10 ⁻³	34,000	—
Complete	2 × 10 ⁻³	36,400	—
Complete	5 × 10 ⁻⁴	35,800	63,200
No Mg ²⁺ , EDTA 10 ⁻³ M	5 × 10 ⁻⁴	1,650	920
Mg ²⁺ 10 ⁻¹ M, EDTA 10 ⁻³ M	5 × 10 ⁻⁴	36,200	70,600
1.0 mg protein	1 × 10 ⁻³	32,800	—
2.0 mg protein	1 × 10 ⁻³	34,000	—
5.0 mg protein	1 × 10 ⁻³	31,200	—
0.65 mg protein	1 × 10 ⁻⁴	—	25,500
1.3 mg protein	1 × 10 ⁻⁴	—	29,300
2.6 mg protein	1 × 10 ⁻⁴	—	31,500
¹⁴ C-SAM 4 × 10 ⁻⁶ M	1 × 10 ⁻³	29,500	—
¹⁴ C-SAM 8 × 10 ⁻⁶ M	1 × 10 ⁻³	43,600	—
¹⁴ C-SAM 2 × 10 ⁻⁵ M	1 × 10 ⁻³	70,800	—
¹⁴ C-SAM 1.65 × 10 ⁻⁶ M	1 × 10 ⁻⁴	—	17,800
¹⁴ C-SAM 3.3 × 10 ⁻⁶ M	1 × 10 ⁻⁴	—	29,600
¹⁴ C-SAM 6.6 × 10 ⁻⁶ M	1 × 10 ⁻⁴	—	48,500
¹⁴ C-SAM 1.65 × 10 ⁻⁵ M	1 × 10 ⁻⁴	—	71,100
II, Human liver (12 h post-mortem)			
¹⁴ C-SAM 2 × 10 ⁻⁵ M	0	608	—
¹⁴ C-SAM 2 × 10 ⁻⁵ M	1 × 10 ⁻³	3,990	—

Complete system: 2 mg protein from 100,000g for 1 h dialysed tissue supernatant, 200 μmol, Tris-HCl buffer, pH 9.0, 10 μmol MgCl₂, 4 μmol ¹⁴C-SAM (specific activity 52.3 mCi/mmol) and the concentration of 4-DMM or NA-4-DMM listed, in a total volume of 1 ml. Incubations at 37° C were carried out for 15 min. All preparations listed are complete except for departures noted. Human tissues were not dialysed. Results are corrected for low blank values obtained without substrate, but are not corrected for recovery.

* All data are rounded to 3 significant figures.

mescaline may be formed by an enzyme different from that involved in the formation of the dimethoxy compounds.

Neither the dimethoxy compounds nor mescaline seem to be formed through the action of any of the O-methyltransferases described by other investigators. Catechol-O-methyltransferase requires that substrates have an adjacent free hydroxy group³. Hydroxy-indole-O-methyltransferase is found only in mammalian pineal gland⁴, and the best substrate for this enzyme, N-acetyl-serotonin, was not methylated in our system. Phenol-O-methyltransferase is found only in the particulate fraction, is inhibited by Mg^{2+} , is not inhibited by 10^{-3} M EDTA, and does not methylate 4-DMM (ref. 5). In addition, we have tested microsomal phenol-O-methyltransferase for activity against both phenol and i-NAMT. Only the former yielded a labelled product (anisole). Another O-methyltransferase, iodophenol-O-methyltransferase, has a low pH optimum, approximately pH 6 (ref. 6), and does not require Mg^{2+} . In contrast, the formation of di-O-methylated compounds proceeds more than 1,000 times as rapidly at pH 9 as at pH 6 and the mescalines are formed more than ten times as rapidly at the higher pH.

Some of the substrates involved in the formation of the dimethoxy compounds are known to be formed by mammalian tissues^{7,8}. Neither 4-DMM nor NA-4-DMM, however, are known in mammalian tissues and no metabolic route for their formation has been established in mammals. A compound, 3-methoxy-4,5-dihydroxyphenethylamine, which could conceivably serve as a precursor of 4-DMM has been reported to be formed by rat and rabbit liver from 3-methoxytyramine. The 3-methoxy-4,5-dihydroxy product, however, was not identified definitely⁹. Also the formation of 5-hydroxy derivatives of other 3-O-methylated catecholamine metabolites has been shown¹⁰. These might serve as a metabolic link between catecholamines and mescaline. It is not known, however, whether any of these reactions have physiological significance or can take place *in vivo*.

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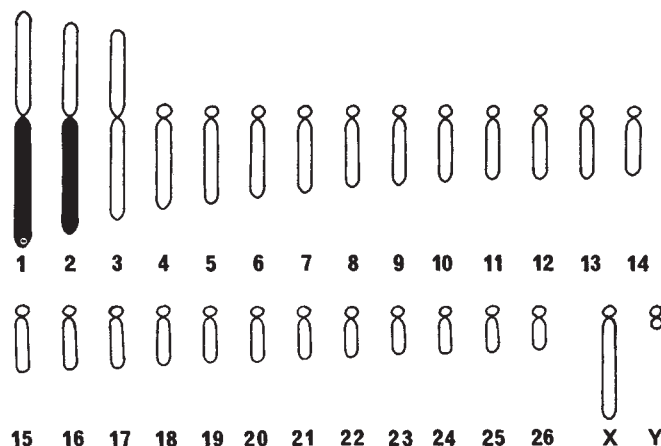


Fig. 1 The twenty-six autosomes of the haploid complement and the sex chromosome pair of the sheep ($2n=54$). The diploid complement has the fundamental number of sixty arm-pairs.

in the males than in the females. Nine spreads were examined from an intersex sheep, a genetic female which had well-developed testes and masculinized genitalia. The lengths of some of the chromosomes in her karyotype resembled those of normal males. The observations may indicate some autosomal control of the differentiation of sex.

The preparation of chromosome spreads from blood lymphocytes and the measurements of length were carried out as previously described¹. The karyotype was treated as sixty arm-pairs and each pair was calculated as its percentage of the total length of chromatin in the spread. The divisor was adjusted in each case so that the male and female karyotypes were comparable. This was done by subtracting the length of the Y chromosome from the total length of chromatin in a male spread; in the females the divisor was the total length of chromatin without the shorter X chromosome. Although these measurements are not in absolute units they provide a useful comparison of the two groups. Also each chromosome of the haploid complement was expressed as a ratio, using the single X chromosome of the males or the longest X chromosome of the females as a divisor.

The chromosomes which showed differences in length are identified in Fig. 1, and the observations are summarized in Tables 1 and 2. The measurements, expressed as percentages, compared each arm-pair with the total length of chromatin in the complement. They showed that the long arms of the first and second metacentric pairs and the fourth pair, which is acrocentric, were longer in the males than in the females. The difference between the males and females in the long arms of the first pair was 0.25% ($0.01 > P > 0.002$); in the long arms of the second pair the difference was 0.19% ($0.02 > P > 0.01$) and the difference between the sexes in the fourth pair of autosomes was 0.09% ($0.05 > d > 0.01$). Six pairs of short acrocentrics were slightly longer in the females than in the males ($0.05 > P > 0.02$). In the nature of percentages, however, surplus length in one part of the range must result in a shortage at another; it may be difficult to judge whether this tendency is the result of real differences in length, or due to a bias introduced by the use of percentages. In the alternative examination of the measurements, it was assumed that the X chromosome of the males and the longest X chromosome of the females are of equal length and ratios were calculated of each autosomal arm to the X chromosome. It was found that the length differences between males and females persisted in the long arms of the first and second pairs of metacentrics, but that the differences among the acrocentrics were no longer significant. Thus both methods of assessment record a greater length in the long arms of the first and second pairs of metacentric chromosomes in the males. These observations are consistent with the presence of male-determining genes on the long arms of the first two pairs of autosomes. (These arms

Difference in Chromosome Lengths between Male and Female Sheep

A STUDY of the lengths of the chromosomes in sheep and goats¹ suggested incidentally that there are small differences between the sexes in the lengths of some chromosome pairs. Here I report the measurement of thirty chromosome spreads from thirteen genetically normal male sheep and thirty-one spreads from thirteen normal ewes, showing differences between the sexes in two pairs of large autosomes which were longer

have been shaded in Fig. 1.) The intersex animal, a genetic female, provided support for this theory in the form of its karyotype. The long arms of the first pair of metacentrics were significantly longer than those of normal females and compared with the length of the male pair. Unfortunately, only nine measurable spreads could be found, and, as the animal is now dead, no more can be done. It may be that a genetic fault caused elongation of those regions of the chromosomes which would normally be contracted and inactive in the female, so that male-determining sequences were brought into use. This evidence suggests that a measurable part of the autosomal chromatin controls the determination of sex.

Alternative hypotheses can be suggested to account for this situation. (1) During the evolution of the *X* and *Y* chromosomes from an identical pair of sex chromosomes, structural genes for the reproductive system were developed from redundant sequences on existing autosomes^{2,3}. This would compensate the male for loss of such material during the reduction of one of the original sex chromosomes to form a small *Y* chromosome. (2) One of the original pair of identical sex chromosomes was subdivided to form the *Y* chromosome, together with other fragments which were distributed by translocation among

the autosomes. These fragments would resemble the other sex chromosomes (an *X* chromosome) in bearing genes for sex determination^{4,5}. The inheritance of the translocated chromatin would be exactly as it is in the case of all other autosomal material. Both sexes would possess a full complement of the genes concerned and crossing over would be no hindrance to their function. The active use of these genes would be decided by the presence or absence of a *Y* chromosome elsewhere in the complement. The excessive length of the long arms of the metacentric chromosomes suggests that the male is making use of genes which in the normal female are inactive. The normal female would possess these genes although she would make no use of them. Is it possible that such a re-distribution of sex-determining genes among the autosomes has provided sufficient genetic material there to constitute the equivalent of an *X* chromosome? In such a case lyonizing⁶ of an *X* chromosome in the female would occur, not because it is the second but because it is effectively the third *X* chromosome of the complement.

Both the first and second hypotheses are supported by the fact that vertebrates which have identical sex chromosomes lack sex chromatin. Those fish, amphibians and reptiles

Table 1 Showing the Length of Chromosome Pairs expressed as Percentages of the Total Length of Chromatin in the Karyotype

Chromosome pair	♂	Length % of total chromatin ♀	♂-♀	P	Intersex	Length % of total chromatin ♀	Intersex-♀	P
Long arms of 1	5.83	5.58	0.25	<0.01 >0.002	6.09	5.58	0.51	<i>d</i> ~0.05
Long arms of 2	5.11	4.93	0.18	<0.02 >0.01	5.01	4.93	0.08	>0.25
4	4.59	4.50	0.09	<i>d</i> <0.05 >0.01	4.66	4.50	0.16	<0.01 >0.002
<i>X/X</i> ₁	2.55	2.56	-0.01	>0.25	2.60	2.56	0.04	>0.25
15	2.94	2.99	-0.05	<0.05 >0.02	2.90	2.99	-0.09	<0.02 >0.01
16	2.85	2.90	-0.05	<0.02 >0.01	2.84	2.90	-0.06	<0.1 >0.05
17	2.77	2.83	-0.06	<0.02 >0.01	2.75	2.83	-0.08	<0.05 >0.02
22	2.27	2.33	-0.06	<0.05 >0.02	2.23	2.33	-0.10	<0.05 >0.02
23	2.18	2.24	-0.06	<0.02 >0.01	2.12	2.24	-0.12	<0.02 >0.01
25	1.99	2.06	-0.07	<0.05 >0.02	1.89	2.06	-0.17	<0.01 >0.002

Table 2 Showing the Length of the Autosomes expressed as a Proportion of the Length of the *X* Chromosome

Chromosome pair	♂	Length of autosomes Length of <i>X/X</i> ₁ ♀	♂-♀	P	Intersex	Length of autosomes Length of <i>X/X</i> ₁ ♀	Intersex-♀	P
Long arms of 1	1.14	1.09	0.05	<0.01 >0.002	1.17	1.09	0.08	<0.01 >0.002
Long arms of 2	1.00	0.96	0.04	<0.05 >0.02	0.97	0.96	0.01	>0.25
4	0.90	0.88	0.02	<0.25 >0.1	0.90	0.88	0.02	>0.25
15	0.58	0.58	0.00	>0.25	0.56	0.58	-0.02	<0.25 >0.1
16	0.56	0.57	-0.01	>0.25	0.55	0.57	-0.02	<0.25 >0.1
17	0.55	0.55	0.00	>0.25	0.53	0.55	-0.02	<0.25 >0.1
22	0.45	0.46	-0.01	>0.25	0.43	0.46	-0.03	<0.25 >0.1
23	0.43	0.44	-0.01	<0.25 >0.1	0.41	0.44	-0.03	<0.1 >0.05
25	0.39	0.40	-0.01	<0.25 >0.1	0.37	0.40	-0.03	~0.02

which have no sex chromatin could be assumed not to have acquired an "autosomal X chromosome" as they have not evolved a sex chromosome constitution of the mammalian type. There would be no extra genes to suppress.

Perhaps it should be added that an "autosomal X" would be a separate entity from the other X chromosomes and that any other genetic characters, if they were present, would show the normal autosomal pattern of inheritance and need not therefore be detectable as sex-linked genes.

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Termite Queen Substance : 9-Oxodec-*trans*-2-enoic Acid

EXTRACTS of honeybee (*Apis mellifera*) queens inhibit the development of supplementary reproductives in the termite, *Kaloterme flavicollis*¹. Similarly, extracts of a whole queen of the termite, *Odontotermes* genus², and queen heads of *O. assmuthi* inhibit queen rearing by workers of *A. mellifera*² and *A. cerana* (unpublished work of A. S. *et al.*) and also development of the workers' ovaries of these species. These observations indicate that the "queen substance" of honeybees and termites exhibits reciprocal activity, and suggest that the chemical nature of the queen substance of termites may be 9-oxodec-*trans*-2-enoic acid of *A. mellifera*³, *A. cerana*, *A. dorsata*^{4,5} and *A. florea*⁵ or a similar substance; but the queens of termites have not yet been unequivocally shown to contain queen substance. We have made extracts of physogastric queen heads of the mound-building termite, *O. assmuthi*, and have analysed these extracts qualitatively for queen substance.

Seventy-nine physogastric queens of *O. assmuthi*, which were of different ages, were collected from several termitaria in Dharwar, Mysore State, India. Their heads were severed with clean forceps and dropped directly into diethyl ether in a screw-capped vial. The vial containing the queen heads in diethyl ether was mailed to the United States for chemical analysis. The vial was opened and the heads were well crushed and extracted with two portions of diethyl ether. The ether extract was methylated by heating in a steam bath for 10 min with 0.5 ml. of 12.5% boron trifluoride in methanol. Water was then added and the mixture extracted with ether (3 × 0.5 ml.). The ether layer was washed and dried over anhydrous sodium sulphate and evaporated totally. The residue was taken up in suitable amounts of petroleum ether, and submitted to Perkin-Elmer 900 model gas chromatography using a flame ionization detector. Two different glass columns (8 feet × 1/8 inch) containing (1) 5% 'Apiezon M' and 1% DEGS (diethylene glycol succinate) on 70/80 'Chromosorb G' and (2) 10% DEGS on 60/80 'Gas Chrom Z' were used. Peak heights and retention times were compared using a standard solution of synthetic 9-oxodec-*trans*-2-enoic acid (OEA) after methylation by the above-mentioned method.

For infrared analysis, the methylated samples of termite queen head extracts and OEA were chromatographed separately and collected at the column outlet by the use of a splitting device. A fraction from each sample was trapped in a length of glass capillary tubing and rinsed out with a few microlitres of carbon tetrachloride and transferred to a microcavity cell.

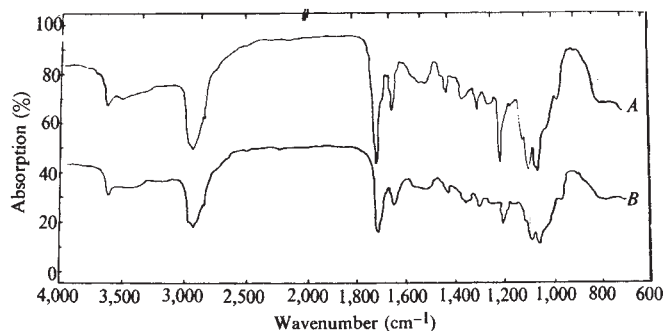


Fig. 1 Infrared spectra of methylated synthetic queen substance (A) and isolated from queens of *Odontotermes assmuthi* (B) in carbon tetrachloride.

The infrared spectra were obtained using a Perkin-Elmer IR 10 spectrophotometer equipped with a beam condenser.

The methylated extracts from queen heads of *O. assmuthi*, and sample of OEA which had been methylated, were subjected to gas chromatography in the two different columns. The extract showed one peak predominantly. The retention time of the peaks on each of the columns matched closely with those obtained from the methylated OEA.

The infrared spectra (Fig. 1) of the fraction collected from the gas chromatogram was identical in all major respects, and corresponded to the spectrum of the methylated OEA collected from the gas chromatogram and analysed in the same way.

These data indicate that the physogastric queens of the termite, *O. assmuthi*, also produce OEA like the queens of *Apis* species³⁻⁵. A point of interest is that though termites (Isoptera) and honeybees (Hymenoptera) occupy different orders of the class Insecta, both have evolved a social mode of life, and the queens of both orders have developed the same pheromonal molecule to perform the common colonial functions. In other words, the social mode of life and OEA might have developed concurrently by convergent evolution of social insects.

It is well established that OEA of the queens of *Apis* species³⁻⁶ inhibits queen-rearing by workers and development of workers' ovaries, and also serves as a sex attractant. It remains to be seen whether all these functions are performed by the "queen substance" of termite queens in the termite colony. Further work is in progress to investigate whether OEA is present in other sources of physogastric queens, such as abdominal spiracular exudate, anal exudate and collateral gland secretion, the results of which may illuminate the role(s) of queen substance in the social biology of termites.

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Delayed Effects of Juvenile Hormone on Insect Metamorphosis are mediated by the Corpus Allatum

EXPOSURE of insect embryos to juvenile hormone or to any of its analogues can result in delayed effects which are realized later at metamorphosis¹⁻⁵. These have been attributed to: (1) persistence of the applied hormone through larval life²; (2) interference with the overall programming of the embryo for postembryonic development^{1,3}; and (3) the selective interference with the embryonic programming of the corpus allatum^{3,5,6}. This study presents evidence that juvenile hormone disrupts the embryonic programming of the corpus allatum such that it does not cease secretion of the hormone as a prelude to metamorphosis.

Eggs of the linden bug, *Pyrrhocoris apterus*, were exposed to a mixture of juvenile hormone analogues⁷ 1.5 days before hatching. A solution of 2.5 µg of the analogues in 0.1 µl. of acetone (Mallinkrodt 'Nanograde') was applied to each egg⁸. Eggs were placed in 100 mm plastic Petri dishes lined with Whatman No. 1 filter paper (20 eggs per dish) and supplied with linden seeds and water. Unhatched eggs and shells were removed the day after hatching, and shed skins were removed after each moult. Larvae (hereafter referred to as treated larvae) were moved to new dishes after the moult to the third and to the fifth instar.

Larvae destined for surgical manipulations were deprived of food within 6 h of the moult to the fifth (last) instar. Twenty-four hours later, the corpus allatum was removed with fine forceps through a transverse slit in the neck membrane. The gland was then implanted through a slit in the metathoracic pleuron of a recipient of similar age.

As seen in Table 1, 72% of the treated *Pyrrhocoris* larvae formed adultoids which showed effects ranging from a marked juvenilization of the wings to the formation of supernumerary sixth instar larvae. By contrast, untreated larvae in similar conditions consistently formed normal adults.

Allatectomy of the treated fifth instar larvae reversed the effects of the prior treatment with juvenile hormone (Table 1, Fig. 1). Of thirty-two animals which were allatectomized, twenty-seven formed externally normal adults, although the females in this group failed to mature eggs. Thus, the complete removal of the gland was confirmed, since *Pyrrhocoris* requires the corpus allatum for vitellogenesis⁹. The remaining five animals showed only minor juvenilization of the wings, although autopsy revealed no trace of the corpus allatum.

The endocrine activity of the corpus allatum was determined by gland implantation. As seen in Table 1, glands from larvae at the outset of the fifth instar were inactive¹⁰. By contrast, corpus allatum from treated larvae produced 51% adultoids.

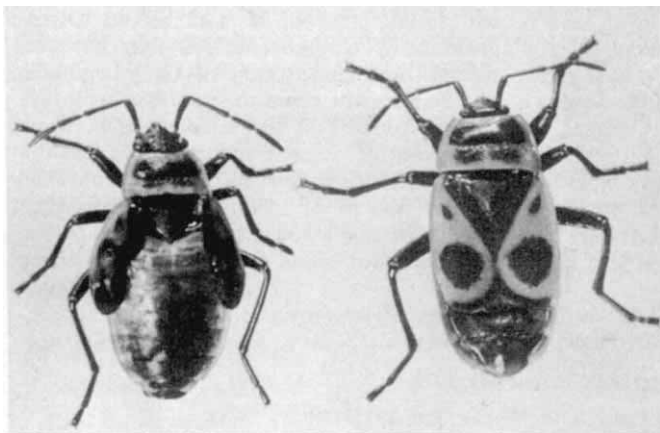


Fig. 1 Left, an untreated individual which had received the corpus allatum from the treated animal on the right at the outset of the fifth instar. The larval type wings and the red patches of larval cuticle on the ventral abdomen classify it as a +2 adultoid. Right, an externally normal *Pyrrhocoris* adult which was treated with the mixture of juvenile hormone analogues as a late embryo. It was allatectomized after the moult to the fifth instar.

The recipients showed effects which ranged up to the reformation of large patches of larval cuticle on the abdomen (Fig. 1). But these effects were not as marked as those in the donors. Similarly, removal and reimplantation of the corpus allatum of five treated larvae caused decreased juvenilization (Table 1). To test the effectiveness of transplanted glands, active corpora allata of fourth instar larvae were used; the recipients showed effects ranging from supernumerary larvae to normal adults, thus indicating the problems inherent in transplantation.

The results reported here are consistent with the experiments of Willis and Lawrence which involved grafts of integument between treated and untreated *Oncopeltus*². Contamination due to rearing treated larvae in the same cage throughout larval life may account for their "bristle-oriented patches" of larval cuticle, which was the evidence for the conclusion that the delayed effects arise from persistence of applied hormone². When treated *Pyrrhocoris* are left in the same dish throughout larval life, there is a slight enhancement of juvenilizing effects which we presume arises from juvenile hormone analogues or active metabolites in the excreta and cast skins.

These experiments, therefore, show that juvenile hormone can somehow interfere with the programming of the embryonic corpus allatum. This gland then fails to cease secretion of the hormone at the outset of the last larval instar.

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Table 1 Application of Juvenile Hormone Analogues to Late *Pyrrhocoris* Embryos: Effects on the Function of the Corpus Allatum at the Outset of the Fifth Instar

Treatment of embryo	Treatment of fifth instar larva	No.	Normal adults (%)	Adultoids (%) [*]				
				+1	+2	+3	+4	+5
None	None	713	100	0	0	0	0	0
JHA	None	54	28	11	20	13	24	4
JHA	Excise and reimplant CA	5	40	20	20	20	0	0
JHA	Excise CA	32	84	16	0	0	0	0
None	Implant CA from fifth instar larvae treated with JHA as embryo	59	49	29	22	0	0	0
None	Implant CA from untreated fifth instar larva	67	100	0	0	0	0	0

JHA, juvenile hormone analogues; CA, corpus allatum.

^{*} The classification of adultoids was based on the scoring system of Williams and Sláma⁸.

0, Normal adult; +5, supernumerary sixth instar larva.

Some Effects of Stress in the Adult on the Larval Development of *Mytilus edulis*

ONCE triggered by temperature and food stimuli, vitellogenesis in bivalve molluscs proceeds to completion in spite of sub-optimal environmental conditions^{1,2}. Following maturation, however, disintegration of gametes occurs unless further stimuli are received to initiate their release from the animal (spawning), which poses the question, how are the larvae that develop from gametes produced in sub-optimal conditions affected by the stress experienced by the adult?

Experiments were carried out to follow the effects of temperature and nutritive stress on the mussel, *Mytilus edulis*. The mussels were maintained at 15° C and 30.5 ± 2.4 mg dry weight of phytoplankton cells per animal per day. The effects of these conditions on the adults have been discussed elsewhere^{3,4}. At the end of the experimental period, animals were given a spawning stimulus of 5° C temperature increase followed by injection into the posterior adductor muscle of 1 ml. 0.5 M KCl. Animals collected 3 days previously from a field population were treated similarly as controls. In September and December, animals could not be induced to release gametes due to the early stage of gametogenesis, but in April and June (after 85 and 54 days of stress respectively) animals were stimulated to spawn, and the development and growth of their larvae followed at 16° C and 18‰ Cl. Methods for encouraging fertilization and subsequent development have been described previously⁵. The prodissoconch larvae were fed *Tetraselmis suecica* at 50 cells µl.⁻¹.

following the onset of feeding at the prodissoconch II larval stage.

The development of the embryos of bivalve molluscs broadly comprises three stages. Stage 1 includes cleavage of the egg, gastrulation and embryogenesis to the prodissoconch I larva. This is followed by a period of growth as the prodissoconch II shell is deposited and the velum and visceral mass increase in size. The third stage is initiated by the development of the foot and the primary gill filaments, and is terminated by settlement and metamorphosis to the young adult⁶. Stages 1 and 3 represent periods of intense morphogenetic activity, when new organs are developed, but little increase in size occurs. There is also a greater reliance on stored food reserves than in larvae at stage 2: these reserves accrue to stage 1 larvae from the adult and to stage 3 as a result of feeding in the planktotrophic phase (stage 2). Stage 2, however, represents a period of minimal development of new organs, but of considerable growth as the larva increases in length from 110 to 250 nm. Recognition of these stages suggests that sub-lethal temperature and nutritive stressors on the adult have a measurable effect on the larval development during periods of maximum morphogenetic activity, and a minimal effect during the main phase of larval growth. This interpretation predicts a further period of "failure" in the development of larvae from stressed adults at the time of metamorphosis. A recent study by Stephenson and Helm⁷ on larvae of the oyster, *Ostrea edulis*, confirms this prediction.

Although development of the oocytes, vitellogenesis, spawning and fertilization seem to proceed normally in bivalves under sub-lethal stress, changes occur which result in the increased occurrence of abnormal embryological develop-

Table 1 Larval Development and Growth following the Spawning of Stressed (Experimental) and Unstressed (Control) Adult *Mytilus edulis*

Experiment No.	Spawning success % (n)	Fertilization success % (n)	Abnormal cleavage % (n)	Abnormal trochophore % (n)	Normal prodissoconch I % (n)	Daily growth (nm)
1 April						
Experimentals	24 (55)	94 (259)	28 (322)	41 (322)	29 (344)	6.8
Controls	28 (23)	99 (242)	3 (241)	19 (241)	78 (260)	7.8
P	<0.25 >0.10	<0.95 >0.90	<0.005	<0.005	<0.005	<0.90 >0.75
2 June						
Experimentals	21 (40)	86 (69)	24 (130)	71 (195)	29 (235)	6.5
Controls	23 (35)	90 (100)	8 (67)	33 (81)	70 (91)	6.8
P	<0.90 >0.75	<0.975 >0.95	<0.005	<0.005	<0.005	<0.975 >0.95

The numbers in parentheses are the numbers of observations. P is the probability that the observed values for the experimentals and the controls were taken from the same statistical population, as determined by a χ^2 test.

There was no difference in the number of animals that spawned in the stressed (experimental) and unstressed (control) groups (Table 1), although stressed females released fewer eggs than the control females. The proportion of eggs successfully fertilized did not differ between experimental and control groups. The following conditions were then assessed during subsequent development: 1, the proportion of abnormal cleavage stages observed after 4 h, recognized by failure to form the polar lobes; 2, the proportion of abnormal trochophores counted after 12 h, recognized by abnormal ciliation and progress through the water; 3, the proportion of normal prodissoconch veliger larvae present after 48 h, recognized by shape and dimensions of the shell and by the mode of swimming; 4, the daily growth of the shelled veliger larvae, which was followed for 5 days after fertilization.

There was a higher percentage of abnormal cleavage stages in the experimental cultures than in controls (Table 1). A larger proportion of abnormal trochophores developed in the cultures derived from stressed adults, and this was reflected later in a smaller proportion of normal prodissoconch I larvae. The two groups did not, however, differ in rate of growth

ment. Further studies are necessary to characterize this apparent loss of quality in gametes from stressed adults, and to identify the causes as being either nuclear or cytoplasmic.

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Plutonium and Polonium inside Giant Brown Algae

ALTHOUGH plutonium is an extremely toxic radioactive element^{1,2} and has at least two long lived nuclides—²³⁹Pu ($t_{1/2}$ = 24,000 yr) and ²³⁸Pu ($t_{1/2}$ = 88 yr)—little is known of how it becomes dispersed; too few measurements have been made in particular in marine environments.

Background levels of plutonium in the ocean were first determined³ at this laboratory in 1964 (see also refs. 4 and 5) when it emerged that certain marine algae accumulated plutonium so effectively that they might be used to detect small concentration changes in seawater that would be difficult to measure directly. Sessile algae are especially useful as monitoring aids because they can be sampled repeatedly. High concentrations of plutonium in bulk samples of algae have since been reported in widely separated oceanic areas, especially in floating plants collected from the central Atlantic⁶.

Organisms in the marine environment near here were resurveyed⁷ in 1971, after reports that a nearby coastal power reactor had received several fuel rods containing plutonium. Activity concentrations of plutonium and other nuclides were compared in selected specimens of brown, red, and green sessile alga, and in marine grasses. Large accumulations were found in several species, but concentrations ranged widely within species suggesting a correlation between activity and surface area. Therefore attention was turned to comparing different tissues of one giant brown alga, *Pelagophycus porra* (elk kelp), growing beyond the surf lines of California. Two other giant kelp species were also dissected for comparison. The samples dissected for plutonium analysis by alpha spectrometry were also analysed for ²¹⁰Po, a natural alpha emitter which is more highly concentrated in seawater than plutonium but seems to behave similarly in tissues of brown algae. It was hoped that the distribution of ²¹⁰Po might serve as a model for predicting distributions of the less easily analysed ²³⁹Pu and certain other heavy metals such as stable lead in marine plants. Moreover, polonium is also of interest because it is an important contributor to the natural radiation background of living organisms⁸⁻¹⁰.

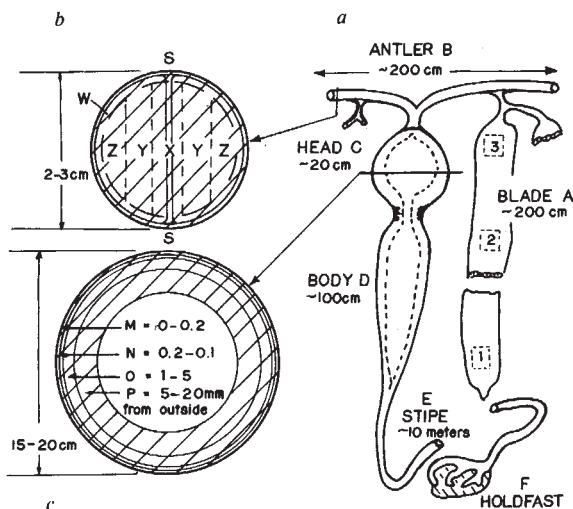


Fig. 1 a, Regions sampled in the giant brown alga, *Pelagophycus porra*. One blade (A) was sampled by cutting out the 10 cm × 10 cm areas, 1, 2 and 3. The whole antler (B) was composited, and also analysed in separate layers (W, X, Y, and Z) as shown in b. The head and body were composited, and also analysed on separate layers as shown in c. The numbers indicate sub-samples listed in Table 1 and Table 2. b, The antler is solid but exhibits a distinct discoloured band S-S. Therefore, the outside layer (W) was removed (about 1 mm thick), and layers (X, Y, and Z) were taken parallel to the tissue S-S. c, The thick walls of the hollow head and body members were sectioned in concentric layers. A thin outer layer (M) was scraped off (roughly 0.2 mm); on other specimens a layer (N) about 1.0 mm thick was removed with a potato peeling knife, then two thicker layers (O and P) were cut out.

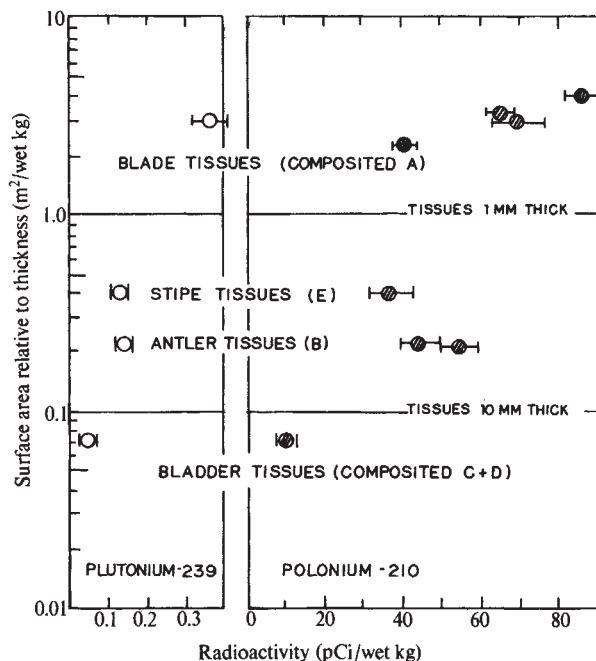


Fig. 2 ²³⁹Pu and ²¹⁰Po concentration range in different parts of the giant brown alga *Pelagophycus porra* identified in Fig. 1a. Concentrations (wet basis) here are averaged over the entire organ; much higher concentrations are found in thin tissues (see Table 2).

Fig. 1a-c shows the parts of *Pelagophycus porra* that were sampled. Only one of the twelve to twenty blades is shown. Two other brown algae were also sampled, species of *Eisenia* and *Pterygophora*. Both have perennial solid stipes¹¹ that can be sampled in layers and the latter is reported¹² to live for possibly 25 years and exhibits what are called "annual rings". Analytical details are available for the alpha analysis of biological materials for ²¹⁰Po (ref. 13) and ²³⁹Pu (ref. 14).

Distributions of ²³⁹Pu and ²¹⁰Po in several *Pelagophycus porra* are shown in Table 1. On a wet weight basis, ²¹⁰Po concentrations varied significantly between morphologically different parts of this plant, and even between different sections of the same part. For example, greater activity is found near the distal end of the blade than near the stem end.

Activities in different layers of antler and bladder tissue of the *Pelagophycus* samples are listed in Table 2. Here again in any given layer different activity densities of ²¹⁰Po are evident. Polonium concentrations in the outermost thin layer, M, are 1,000 times greater than that found in the inner layers, O and P. The highest concentration of ²³⁹Pu also was found in the outer layer; however, the apparent outside-to-inside ratio of 200 : 1 is less striking. It must be pointed out, however, that because only extremely small concentrations of plutonium and polonium were found inside this alga, it is possible that during sectioning the much cleaner inner tissues might have become contaminated from the relatively higher concentrations present in the outer surfaces. In other words, these preliminary measurements do not deny the possibility that the outside-to-inside ratios of plutonium and polonium may be still higher.

Fig. 2 summarizes some of the consequences of sampling different parts of *Pelagophycus porra*, for example, for the purpose of making sensitive inferences about environmental concentrations of ²³⁹Pu and ²¹⁰Po. A sample from a composite of blade tissue yields about ten times more countable activity than an equal weight of bladder tissue. Table 2 indicates that the analytical sensitivity then might be increased by still another factor of 40 above the sensitivity from sampling blades when the 0.2 mm outermost tissue is used. Tables 1 and 2 show that the outermost layers of the *Pelagophycus* had built up ²¹⁰Po concentrations to about 90,000-fold and ²³⁹Pu to about 3,000-fold relative to seawater. On the other hand, the

Table 1 ^{210}Po and ^{239}Pu Concentrations found in Different Parts of *Pelagophycus porra*

Sample	Description (see Fig. 1a)	Collection date (1971) *	Relative surface area m ² /kg	^{210}Po (pCi/kg wet) †	^{239}Pu (pCi/kg wet) †
A Blade	(1) Tip	Aug.	—	105 ± 8	—
	(1) Tip	Oct.	4.0	87 ± 5	—
	(2) Middle	Oct.	3.2	65 ± 3	—
	(3) Near stem	Aug.	—	56 ± 5	—
	(3) Near stem	Oct.	2.6	41 ± 2	—
B Antler	Composite	Aug.-Oct.	3.0	70 ± 7	0.36 ± 0.04
	Near stem	Aug.	—	69 ± 8	—
	Main section	Aug.	—	27 ± 2	—
	Composite	Aug.	0.21	55 ± 5	—
	Composite	Oct.	0.22	45 ± 5	0.14 ± 0.01
C, D Bladder	C, D Composite	Oct.	0.07	11 ± 2	0.05 ± 0.01
E Stipe	Top	Aug.	—	29 ± 4	—
	Middle	Aug.	—	42 ± 2	—
	Bottom	Aug.	—	41 ± 2	—
	Composite	Aug.	0.40	37 ± 5	0.13 ± 0.02
F Holdfast	Composite	Aug.	—	41 ± 2	—
Weighted average of whole plant ‡				35 ± 4	0.14 ± 0.02
Recent seawater—southern California§				0.03 ± 0.01	0.0006 ± 0.0002

* These samples were estimated about 1 yr old.

† The listed errors are the standard deviations of counting alphas.

‡ The weighted average of whole plant was approximated by the following weight percentages: blade, 20%; antler, 15%; bladder, 40%; stipe, 20%; holdfast, 5%.

§ Collected at the Scripps Pier and analysed at this laboratory.

concentration factors derived by analysing whole parts of the plant, especially the thicker parts, are much less sensitive. Thus, it seems that, when comparing two different environments, it is not sufficient merely to sample a given species, but identical sample tissue must be compared. This implies, of course, that something definite must be known about growth rate and behaviour of the species sampled. These measurements not only direct attention toward a need for more rational sampling procedures, but also provoke much curiosity as to why elements so chemically unlike as plutonium and polonium should become accumulated and distributed so similarly in brown algae.

Table 2 ^{210}Po and ^{239}Pu Concentrations found on Surface Layers and in Inner Tissue of *Pelagophycus porra*

Sample	Collection date (1971) *	Sample depth (from outside) mm	^{210}Po (pCi/kg wet) †	^{239}Pu (pCi/kg wet) †
B Antler (Fig. 1b)	W Aug.	0-1	230 ± 22	—
	W Oct.	0-1	200 ± 14	—
	Z Oct.	1-3	6 ± 2	—
	Y Oct.	3-5	4 ± 1	—
	X Oct.	5-10	2 ± 1	—
C, D Bladder (Fig. 1c)	M Nov.	0-0.2	2,800 ± 160	2.16 ± 0.15
	M Oct.	0-0.2	2,400 ± 130	—
	M+N Aug.	0-1	118 ± 10	0.29 ± 0.02
	N Oct.	0.2-1	110 ± 9	—
	N Oct.	0.2-1	94 ± 7	—
	N Oct.	0.2-1	92 ± 7	—
	N Oct.	0.2-1	89 ± 6	—
	O Aug.	1-5	2 ± 1	0.02 ± 0.01
	P Aug.	5-20	3 ± 1	0.01 ± 0.01
	O+P Oct.	1-20	2 ± 1	0.01 ± 0.01

* August and October samples were believed about 1 yr old, November sample older than 2 yr.

† The listed errors are standard deviations of counting alphas.

A first glance at Fig. 2 might suggest that all the activity might be in the outer layers. Fig. 2 indicates that, to the first approximation, radioactive concentrations of these two heavy elements in trace amounts vary linearly with the logarithm of the reciprocal of the thickness of the tissue that is analysed. This type of trend is not entirely consistent with a simple

model in which all the activity is confined entirely within an extremely thin outer layer. A logarithmic trend suggests that some slight inward penetration may take place, perhaps by diffusion, or that some activity is left behind during outward growth.

Data in Table 2 suggest that very little radioactive lead is to be found deep inside of the giant alga *Pelagophycus* as shown by the small amount of ^{210}Po found in the approximately one-year-old inner tissues. During two half-lives of ^{210}Po , any unsupported ^{210}Po would diminish by 75%; however, any ^{210}Pb originally present would have ingrown ^{210}Po equal to 75% of the ^{210}Pb . This suggests a further possibility that all lead, including traces of stable lead, naturally occurring or man-made pollutants, might also be found in only very small amounts inside this alga.

Table 3 Comparisons of ^{210}Po in Different Brown Algae

Species *	Tissues used	^{210}Po (pCi/kg wet) †	
		Inner tissue	Outer layers
<i>Pelagophycus porra</i>	Bladder walls	2 ± 1	118 ± 10 outer 1 mm ~2,800 outer 2/10 mm
<i>Eisenia arborea</i>	Solid stipe	12 ± 3	140 ± 5 outer 1 mm
<i>Pterygophora californica</i>	Solid stipe	46 ± 6	345 ± 30 outer 1/2 mm

* The ^{210}Po concentrations of the composited leaves of the samples of *Pelagophycus*, *Eisenia*, and *Pterygophora* are respectively 70 ± 7, 177 ± 8, and 159 ± 10 pCi/kg wet. In 1965, Folsom *et al.* reported ^{210}Po concentrations of 173.5 ± 12.0 pCi/kg wet in thin blades of *Eisenia arborea* from La Jolla.

† The listed errors are standard deviations of counting alphas.

Table 3 shows that two other giant kelps also accumulate highest activities of ^{210}Po in the outer layers. Finding somewhat more ^{210}Po inside the perennial stalks of the two longer lived algae listed in Table 3 is in agreement with the hypothesis of the inward diffusion of lead or polonium. This also suggests that certain growth characteristics of algae might be studied by making use of these natural radionuclides such as age dating.

The convenience and analytical sensitivity afforded by algal samples for determining ratios of nuclides of plutonium were

demonstrated in 1964 when 780 g of the blades of *Eisenia arborea* were collected for determining the very small traces of ^{238}Pu present in the coastal environment. This sample provided counting activity equivalent to 1,080 times the volume or 840 l. of seawater. Miyake and Sugimura⁵ collected samples of seawater almost this large (500 l.) for their survey of ^{238}Pu in Pacific seawater.

The data reported here suggest that still smaller algae samples may suffice when only thin outermost layers are selected. For example, using only 120 g of wet material scraped from the outer surfaces of thick members of *Pelagophycus porra*, a ratio of $^{238}\text{Pu}/^{239}\text{Pu}$ of 0.055 ± 0.019 was determined recently. This, together with a measurement of ^{239}Pu determined in local seawater (0.0006 ± 0.0002 pCi/kg), indicates a contemporary environmental concentration of ^{238}Pu of 0.000033 ± 0.000011 pCi/kg. It is interesting that this concentration is slightly higher, though hardly significantly, than the 1964 concentration reported³ for the same coastal Northern Pacific region at a date just before the reported¹⁵ accidental burn-up of a satellite carrying 17,000 Ci of ^{238}Pu .

In conclusion, sampling thin parts of brown algae, or thin outer layers, should provide great sensitivity for detecting early changes in the extremely small traces of plutonium that are now anticipated in the sea from reactor effluents, nuclear fuel processing or fallout. Because of these intense local sources of alpha activity on the outermost surface, it is evident that they must contribute substantially to the natural burdens of radiation experienced by some organisms associated with algal surfaces. The extreme variation in concentrations, more than 1,000-fold, observed within brown algae emphasizes that samplings must be identified more carefully as to specific tissue types, and casts doubt as to the usefulness of many concentrations reported in the past.

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Permian Reptilian Fauna from India

THE Indian Gondwana formations are continental sediments which range in age from early Permian to about the middle of the Cretaceous. They have yielded a number of tetrapod faunas, mostly from Triassic and early Jurassic formations. Peninsular outcrops from Permian beds have yielded two solitary amphibians, *Gondwanosaurus* and *Rhinesuchus*, while a Lower Permian amphibian fauna has been found in Kashmir (*Archegosaurus*, *Actinodon* and *Lysipterygium*). There are no records of Permian reptiles from any part of the Indian subcontinent and, indeed, few Permian reptile faunas are known from any part of the world. This communication describes the discovery of a reptilian fauna from the Indian Permian.

The Permian is important in the history of reptilian evolution, for it is the period during which reptiles underwent their first major adaptive radiation, became abundant and established themselves as the dominant members of land faunas. Present knowledge of them depends chiefly on the vertebrate faunas of North America, Europe and Africa.

The new Indian fauna was discovered in the northern part of the Gondwana outcrop of the Pranhita-Godavari Valley, Deccan, one of the many scattered outcrops of Gondwana rocks in the Indian peninsula. The succession in this region is:

Post-Kamthi formations (definitely Mesozoic)

Kamthi	} early Permian-?Lower Triassic
Barakar	
Talchir	

Barakar is the coal-bearing formation of the sequence and, in this area, consists chiefly of feldspathic sandstones associated with carbonaceous shales and coal. The succeeding Kamthi formation is essentially a sequence of ferruginous and generally non-feldspathic sandstones and siltstones and has no carbonaceous shales. In the northern part of the Pranhita-Godavari Valley, there can be recognized between these distinct lithological groups a third consisting of feldspathic sandstones of Barakar aspect but associated with red and green mudstones and shales. This third group of beds, intercalated between



Fig. 1 The skull of a medium sized endothiodontid (dorsal view).

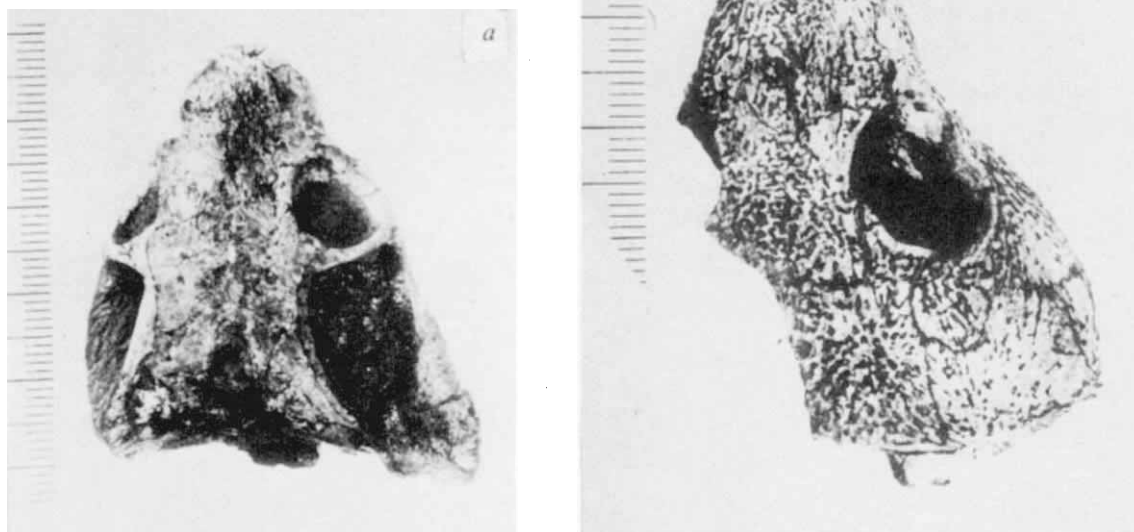


Fig. 2 The skulls of (a) a small dicynodont and (b) a small captorhinomorph (dorsal views); scale in millimetres.

the typical facies of the Kamthi and Barakar formations, has yielded the reptilian fauna. It is of interest that this newly recognized group of beds in the northern part of the Pranhita-Godavari Valley has broad lithological resemblances with the Motur formation which succeeds the Barakar formation in the Gondwana outcrop of the Satpura basin, some 200 miles to the north.

Fossils were mostly found in hard red ferruginous nodules and appear to be locally abundant. Three good localities were found, all of which had abundant surface material consisting mainly of broken-up fossiliferous nodules, which is why identification of much of the surface material was difficult. Nevertheless, about seven vertebrae and some limb-bone fragments were recognized as post-cranial bones. Most of the surface material consisted of skull fragments; a minimum of thirty skulls are represented in the collection. The fact that skulls seen *in situ* material are complete or nearly complete suggests that much of the fragmentation seen in the surface material is a result of recent weathering. The fossils are in general well preserved except for some distortion due to crushing.

The fauna appears to be essentially a dicynodont assemblage. Most of the skull material consists of medium to large endothiodontids, and these include a form (Fig. 1) which is probably a species of the genus *Endothiodon* as characterized by Cox¹. There are also the small dicynodonts, one of which is a tusked endothiodontid represented by a single skull specimen. The other is a tuskless form represented by two specimens, one nearly complete (Fig. 2a). Both have lower jaws in position; whether or not there are cheek teeth is thus uncertain. The skull has a short narrow snout, a wide intertemporal area with wide parietals, no preparietal and a parietal foramen very far back close to the edge of the skull roof, all suggesting possible affinities to *Kistecephalus*. A small captorhinomorph (Fig. 2b) is the only non-dicynodont member so far found in the fauna.

The presence of *Endothiodon* in the fauna suggests straight-away a correlation with the *Endothiodon* zone and, since it may be partly contemporary², to the *Kistecephalus* zone of the Karroo sequence of Africa. Only in these two zones are the medium to large endothiodontids known. A *Kistecephalus*-like form in the new fauna further strengthens this correlation.

Until now the endothiodontids have been known only from the Karroo beds of Africa; thus their extension into India is of some interest, as is the presence of a captorhinomorph in

the fauna. The captorhinomorphs, with the exception of one genus, *Moradisaurus*, from Niger, are known only from North America and Europe, chiefly from lower Permian horizons. Only *Moradisaurus* is known from beds equivalent to the *Endothiodon* and *Kistecephalus* zones, and this is a large form with a mandible about 42 cm long³, while the Indian form is very small with a skull about 5 cm long. The captorhinomorphs are not known in the Karroo faunas and the Indian occurrence is the first association of a captorhinomorph with a dicynodont fauna. Detailed studies of the fauna and stratigraphy are still in progress.

The new fauna was discovered during a field trip to the Pranhita-Godavari Valley Gondwana outcrop with Mr Barry Hughes of the University of Ghana in December 1970. I thank him for his help. I also thank Dr P. L. Robinson and Dr T. Roy-Chowdhury for help and encouragement.

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Late Palaeolithic Dwellings made of Mammoth Bones in South Poland

MANY traces of Palaeolithic settlements can be found in cave sediments, but actual dwellings dating from such ancient times are very rare. Traces of dwellings made of mammoth bones were excavated in Central and Eastern Europe and the Soviet Union in the second half of the nineteenth and early twentieth centuries, as well as a few years ago in the Ukraine. These were the only known settlements of late Palaeolithic mammoth hunters until 1967.

At the end of 1967 fragmentary bones of fossil animals were detected by chance in Cracow, South Poland. Systematic excavations carried out in 1968, 1969, 1970 and 1971 led to the

discovery of a new Palaeolithic site (Fig. 1). Called Krakow, Spadzista Street B, the site lies on a steep rock platform 252.8 m above sea level and about 47 m above the recent valley of Rudawa Stream. The diameter of the rock platform on which the dwellings were built was 40–60 m. The remains of the settlement were covered with a layer of loess 2–3 m thick. The mammoth hunters lived here about 20,000 yr BC—they probably settled there just after the Stillfried B Interstadial.

Three dwellings, built chiefly of mammoth bones, have been discovered so far. More than 90% of the bones belong to *Mammuthus primigenius*. Most of the material used consisted of large bones, especially lower jaws, bladebones (scapulae and pelvis), limb bones, ribs, vertebrae, molar teeth and tusks. Three circles of bones, with diameters of 2.00 to 2.20 m, were distinguished. The distance between the dwellings is about 1 m. The second circle is formed of twenty-three lower jaws. The long bones of the mammoth limbs were oriented from points on the circumference of the circle towards the centre of the dwelling. Badly preserved pairs of tusks, directed W–E, were found near the edge of the dwellings. Inside the circles large pieces of limestone were found. Between the dwellings there were remains of a fireside (or camp fire) and partially burnt bones. Most of the flint artefacts were found at the southern side of the dwellings.

The foregoing suggests that the dwellings were built as follows: the socle (foundation) was formed of lower jaws, bladebones and large limb bones; above them was a construction made of tusks, ribs and vertebrae. The tusks seem to have formed an arch holding together the whole construction. The roof and the walls were probably covered with animal skins (Fig. 2).

Besides the mammoth bones remains of a woolly rhinoceros (*Coelodonta antiquitatis*), a bear (*Ursus* sp.), a horse (*Equus caballus*), a reindeer (*Rangifer tarandus*) and a polar fox (*Alopex lagopus*) were found. The bone material is, in general, well preserved.



Fig. 1 Remains of a late Palaeolithic settlement of mammoth hunters in Cracow, South Poland.

Bones of about sixty mammoth individuals (counted on the basis of the lower jaws) were excavated. Two of these animals were very young—about 2 to 5 yr old—and two were about 50–60 yr old; most were young or semi-adults which probably did not reach sexual maturity. Some of the bones show an abnormal development, for example, ulna and radius are fused (synostosis), molar teeth are twisted, and so on. Many bones, especially metacarpals and metatarsals, show distinct traces of gnawing by carnivores.

More than 1,500 stone artefacts were collected from the site. Most of the artefacts are made of the local Jurassic flint and of flint originating from the northern part of the Kraków–Wielun

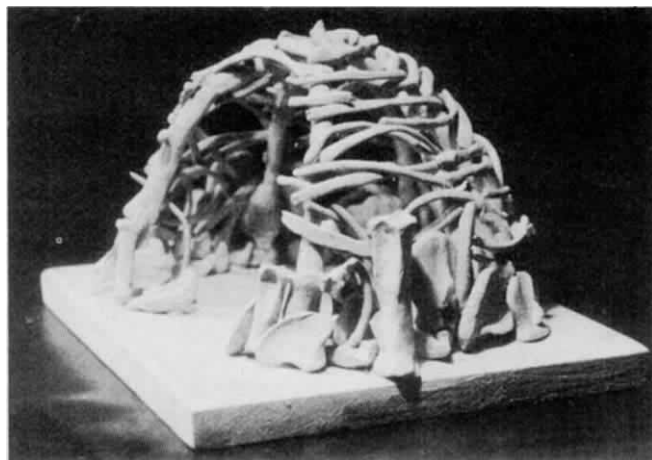


Fig. 2 Reconstruction by G. Zakrzewska of a late Palaeolithic dwelling of mammoth bones.

Jurassic Ridge (about 100 km north of the locality), but some are made of radiolarit from western Slovakia. Among the artefacts are 400 implements, the most numerous being backed blades and *pointes à cran*. Some of these products show flat retouch at the lower side, similar to the Kostienki-type. The second most numerous group consists of burins. End-scrapers occur rather rarely. Retouched blades, as well as cores with one-striking platform and small cores for little blades, were also found. In general these artefacts should be referred to the industry of Vag Valley localities (Moravany, Nitra–Čerman). This attribution is perhaps strengthened by the occurrence of radiolarit from western Slovakia.

Bone products are very rare in the locality in question, though fragments of bones with traces of cutting and planing were found. A *pointe à cran*, which seems to have been used as a knife, was found in one part of a mammoth rib, and we also noticed a few heads of femura and humeri which had been cut and hollowed out. Some of these last could perhaps have been used as lamps.

The stratigraphy and the animal remains from the dwellings of mammoth bones indicated that the site was occupied just after the end of the Stillfried B Interstadial of the last glaciation, or just before the last loess sedimentation of the Pleistocene. The fauna is typical of the Pleistocene steppe-tundra.

The Palaeolithic men living in these dwellings specialized in hunting mammoths from which they acquired meat, bones and skin. More than twenty mammoths were used to build one dwelling. The material took a long time to gather so that the mammoth hunters must have had to stay for a long time at the same place.

The discovery of the late Palaeolithic site in Cracow thus offers many new data concerning these rare sites, dating from the time just before the last loess sedimentation of Würm. The localities where the mammoth hunters lived seem to have been very acceptable to Palaeolithic man because beside the dwellings described here we found the remains of two other cultures dating from before 30,000 yr (Aurignacian) and 17,000–15,000 yr (workshops belonging to the backed-blades industries).

The dwellings made of mammoth bones described here are the first late Palaeolithic remains of such a settlement in Poland and in Central Europe.

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BOOK REVIEWS

Contamination of the Sea

Impingement of Man on the Oceans. Edited by Donald W. Hood. Pp. x+737. (Wiley: New York and London, November 1971). £11.75.

THE vast scale of man's endeavours is revealed by the fact that already the total rate of mining of natural resources is similar to that of rock weathering, and, as Goldberg has pointed out, man has thus become a significant geological agency. A considerable proportion of this material eventually finds its way to the oceans along with enormous amounts of sewage and agricultural waste products and considerable quantities of industrial compounds of many types. Any harmful effects which these materials produce will obviously be much more pronounced where restricted exchange of water allows appreciable concentrations of them to build up. In some such areas toxic elements or compounds have seriously upset the ecology and, in a few instances, human fatalities have resulted through their concentration by organisms used as food. Toxic materials are not the only pollutants endangering aquatic life. If excessive amounts of readily oxidizable organic materials are discharged their decay may reduce the oxygen content of the water to levels at which it will not support the usual forms of life. Such organic matter may arise, for example, from the discharge of untreated sewage, or may be the result of eutrophication brought about by micronutrients entering from sewage or from run-off from agricultural land, particularly after excessive use of fertilizer. Until recently gross pollution has been confined mainly to lakes, estuaries and coastal areas, although some landlocked seas, such as the Baltic and even the North Sea, are now becoming quite seriously affected. The principal ocean areas have so far been little touched by pollution. But the fact that toxic polychlorinated biphenyls occur in zooplankton from the Atlantic at levels of up to 300 parts per thousand million suggests that there is little room for complacency. Work carried out at the Woods Hole Ocean-

ographic Institution implies that the capacity of the deeper waters of the Atlantic to absorb organic wastes may be comparable only with that of the Baltic. The situation in the tropical and sub-tropical Pacific is even more precarious because of the very low oxygen content of the subsurface waters.

There is a growing realization of the dangers which may arise from contamination and pollution of the sea. However, until now, no comprehensive and balanced assessment of the many aspects of the subject has been available. This volume goes a long way towards remedying this deficiency. The editor is to be congratulated on his choice of authors, the uniformly high standard of whose contributions makes it difficult to single out particular chapters for comment. The subject matter is developed logically in six parts. The first of these deals with the natural processes bringing materials into the sea and distributing them in the oceans. The very thorough treatment of horizontal and vertical mixing processes in the sea by A. Okubo gives a most helpful account of the processes involved in the dispersion of dissolved material in the sea. Part II is devoted to a consideration of the chemical systems which control the concentrations and equilibrium status of chemicals finding their way into the sea. Part III is entitled "Artefacts of Man" and gives an account of the principal types of pollutant reaching the oceans, including lead, chlorinated hydrocarbons, petroleum, municipal wastes and heavy metals. Part IV is concerned with the way in which man has influenced the near shore waters by agriculture, engineering and fisheries, etc. Part V deals with models for the present and future distributions of artificial radioactivity in the sea and also with the effects of added nutrients on phytoplankton growth. Legal aspects of marine oil pollution are discussed in the final part, which also includes a colourful historical review of the vagaries of the development (if that is the right word) of US ocean policy. It concludes with an informative summary of the use of the sea as a source of food

and raw materials and as a repository for waste products.

I read the book with great interest and can recommend it to all concerned with marine ecology and pollution. The treatment of the subject matter is sober and factual, and free from the rather hysterical overstatements which are becoming all too common in the discussion of matters concerning pollution. Inevitably, in a book of this kind some sections will be more relevant to the title of the book than others, and the critic might question the need for chapters 8, 15, and 19, which although intrinsically interesting contribute little to the subject of the book. In a volume written by so many authors one might expect to find a great diversity of style and coverage; the scarcity of such defects is a testimony to the careful work of the editor.

J. P. RILEY

Experiments on Embryos

Theories of Differentiation. By Max Hamburger. Pp. x+171. (Edward Arnold: London, November 1971.) £3.50 boards; £1.75 paperback.

THIS book should never have been called *Theories of Differentiation*. Dr Hamburger reviews experiments fairly and clearly but has little space for theories. There are three chapters which make this book a good buy for every university library. These contain good reviews of experiments concerning "Interaction of egg and sperm", "Induction", and "Tissue interaction". These are well written, extensively illustrated, and provided with useful cross references to other review articles. They are valuable because they bring up to date Saxen and Toivonen's *Primary Embryonic Induction*, and because they include a section on the genetic control of inductive interaction. But nothing will be found on recent theories of positional information.

The discussion of "Egg activation", "Gene action and the fate of informational molecules during development",

and "Genetic information and the programming of development" is weak. There are some large gaps here. In the discussion of the increase in protein synthesis after fertilization, no mention is made of experiments published since 1967; this means that theories about inactive polysomes¹ and the rates of chain initiation² are not included. There is an uncritical discussion of RNA synthesis during development; any RNA which cannot be characterized as either ribosomal or transfer RNA seems to be called messenger RNA (mRNA). This may be a misleading guess because it is known that much of the RNA synthesized during cleavage in the sea urchin is broken down in the nucleus³. Many embryologists would think that the best evidence for mRNA synthesis during development comes from studies on the expression of paternal isozymes⁴ but these cases are not included. I would also like to have seen a discussion of cytoplasmic factors in eggs which influence cell differentiation; the polar lobe of *Illyanassa* and the germ cell associated granules of insects and frogs are classical examples which have considerably influenced our thinking about development.

This book should be read for its chapters on induction. It is well produced and good value, particularly as a paperback.

C. F. GRAHAM

¹ Piatogorsky, J., *Biochim. Biophys. Acta*, **166**, 142 (1968).

² Mackintosh, F. R., and Bell, E., *J. Mol. Biol.*, **41**, 365 (1969).

³ Kijima, S., and Wilt, F. H., *J. Mol. Biol.*, **40**, 235 (1969).

⁴ Wright, D. A., and Moyer, F. H., *J. Exp. Zool.*, **163**, 213 (1966).

Scientific Thought

John Dee: The World of an Elizabethan Magus. By Peter J. French. Pp. x+243. (Routledge and Kegan Paul: London, February 1972.) £3.75.

Samuel Johnson and the New Science. By Richard B. Schwartz. Pp. x+188. (University of Wisconsin: Madison, Milwaukee and London, June 1971.) £4.75.

THESE two books are alike in that neither is centrally concerned with the history of science, but with the history of thought in the universal sense, of which natural science is one part. Dr French is concerned with contributions to the formation of the scientific mind of the seventeenth century; Dr Schwartz with the influence of scientific thought upon one of the great literary figures of the eighteenth. Both are books the content of which reflects recent "schools" of history: Dr French's the

history of esoteric ideas developed by D. P. Walker, Frances Yates and Paolo Rossi; Dr Schwartz's the literary history that has revolted against the treatment of Dr Samuel Johnson as an enemy of the scientific culture. Both books are useful studies even though neither is entirely convincing.

Very large claims have been made for John Dee (1527-1608), who was certainly much more than the gullible spirit-botherer popularized by television. He was (it is said) not only a great collector of books, but the master-mind behind the British idea of Empire; a philosopher of naval power, and the practical adviser of the famous Elizabethan navigators; an antiquary of some importance and the most influential English mathematician of his day; a pioneer of the experimental method of science, a master of the art of memory and every other esoteric skill, the friend and equal of the greatest continental intellectuals. Some of the long continued adulation of Dee is certainly justified; he did have an enormous, rich, and scientific library; he was consulted by practical seamen. But sometimes a pinch of salt seems appropriate, though not to Dr French's taste. Some of the stories of his extraordinary feats originate with himself, and a part of his success (as of his troubles) was due to a magical reputation he did nothing to depreciate. He was not above consulting the angels (*via* his medium Edward Kelly) concerning the outcome of voyages of exploration, in the would-be explorer's presence. On the other hand, Dee as a mathematician is known virtually only from his celebrated preface to the English Euclid, a work that shows Dee's eminence as a programmatic writer, but nothing of his technical capacities in the subject.

Verbally, one can resolve most if not all the impossible contradictions involving John Dee by describing him, as Dr French does, as the greatest of the English magi. He was soaked in the mysteries of the cabbala and Renaissance hermeticism. If there is any consistency to be found in the man, it is only by regarding him from a point of view very different from that generally prevalent since about 1700. Dee's universe was founded on an interrelation of matter and spirit in nature analogous to that existing in man himself; man could as well (or better) control nature through its spirit as by working upon its matter directly. Rightly, then, Dr French places Dee in an intellectual milieu very far from the rational but passive tradition of Aristotle and scholastic argument. Like Miss Yates, he argues that the significance of such hermeticism as Dee's is in its activity, in its confidence that man could manipulate nature which (he holds) was transmitted to science.

"What can one make of a man like John Dee?" exclaims Dr French. Dr Schwartz complains that what has been made of Johnson is too simple, too Boswellian (though he does not say this). Johnson, he points out, had read much scientific literature (not including Joseph Priestley, it seems); he wrote a life of Boerhaave; he had quite sensible ideas about electricity and medical practice; he knew the meaning of many scientific terms correctly, and made ether. He was curious about processes of manufacture. He did not believe that the classical world knew everything and the moderns nothing; he was a great admirer of Boyle, Locke, and Newton. In short, Johnson had the typical knowledge and ideas of a cultivated man of his day (including Tories) even if he did not actually, like John Wesley, write scientific pot-boilers himself.

Though one has some doubt about an author who can write that: "Correspondence with Christiaan Huyghens [*sic*] was maintained in spite of the existence of a state of war between England and Holland" and suppose that a *physicien* is a medical man, there is much along these lines well assembled by him. What one may still believe, however, is that Johnson was far more a moralist than a scientist; the proper study of mankind is not nature, as he eloquently insists in the *Life of Savage*, but man. It is moral nature that must be the first object of study, and then physical nature may follow later. Perhaps we ourselves have moved so far from this Johnsonian moral position that it is hardly more readily comprehensible to us than is that of John Dee, the Renaissance magus.

A. RUPERT HALL

All about Lampreys

The Biology of Lampreys. Edited by M. W. Hardisty and I. C. Potter. Vol. 1. Pp. xiv+423. (Academic: New York and London, December 1971.) £7.50; \$22.50.

LAMPREYS and hagfishes are the only living representatives of the most primitive group of vertebrates, the Agnatha, and as such have attracted the attention of evolutionary biologists. Surprisingly, no previous attempt has been made to summarize our knowledge of lamprey biology (although a volume on the hagfish was published almost a decade ago) and to fill this gap Professor Hardisty and Dr Potter have edited a two-volume treatise devoted exclusively to the lampreys. This work has no forerunners or competitors, so one of its functions must be to include all previous information and not just to review more recent advances. This has had the unavoidable conse-

quence of producing a very factual account and the delicate problem of analysis of primitive conditions in a specialized animal has been largely lost in the wealth of information.

In a comprehensive opening chapter, Hubbs and Potter discuss distribution, phylogeny and taxonomy. The remarkable clarity of presentation is slightly marred by small discrepancies in the analytical key for adult lampreys. The typical dentition of the genus *Eudontomyzon* does not quite conform with the diagram of *Eudontomyzon danfordi* and for the subgenus *Lampetra* the shape and distribution of the posterior circumoral teeth are used as diagnostic characters although these teeth are absent. The key is based primarily on dentition, so the problem of ammocoete identification still remains.

The implications of the recently discovered fossil lampreys are discussed by Bardack and Zangerl. But in view of the similarities between this 280-million-year-old fossil and modern lampreys it tells us little of the presumed ostracoderm ancestors of lampreys. The treatment of the origin of the lampreys is very brief and could have been greatly extended.

Two chapters by the editors describe the behaviour, ecology and growth of larval lampreys and the general biology of adult animals. Information has been collected from diverse sources to produce an excellent account which will appeal to the general reader as well as the more serious student of lamprey biology.

Perhaps the greatest stimulus to research into lamprey biology has been the disastrous predation by the landlocked sea lamprey in the Great Lakes. In view of the size and urgency of this problem, many of the data have been collected in less controlled conditions than one would expect of a purely scientific investigation. B. R. Smith has performed a difficult task by selecting from the vast body of information and presenting a clear account of the Great Lakes problem.

One of the more recent trends in lamprey evolution has been the elimination of the parasitic phase to produce the so-called "brook lampreys". Hardisty and Potter, in a well written chapter, have paid particular attention to the evolutionary mechanisms involved and interpret brook lamprey speciation as the result of an extension of the larval phase together with changes in the phasing of gonadogenesis in contrast to the traditional explanation of partial paedomorphosis.

In their introduction to a short chapter on the chromosomes Potter and Robinson emphasize the taxonomic significance of the karyotype. In view of the enormous intraspecific variation and the obvious shortage of data, it is

surprising that this subject has been treated separately. It would have been more useful had the data been presented in the chapters concerned with taxonomy and evolution (chapters 1, 2 and 6).

The cytological aspects of gonadogenesis are well documented by Hardisty although a simplified diagram of gonadal development, based on data from *Lampetra planeri*, would have been a distinct advantage. Limited endocrinological knowledge makes conclusions concerning the control of gonadogenesis very tentative. This first volume is completed by Piavis with an account of lamprey embryology.

In summary, this volume is a well presented, extensive review of the evolution and general biology of the lampreys. Many aspects of physiology and endocrinology are covered in volume 2, and this is in every respect complementary to volume 1. A book of this standard will be an asset to all libraries catering for students of fish biology or vertebrate zoology in general.

ALAN D. PICKERING

Consequences of Science

l'Engagement Social du Scientifique: Conférences du Cinquantenaire de la Faculté des Sciences, Université de Montréal. By Jean-Jacques Salomon, Andre Des Marais and Jean Dorst. Pp. 99. (Université de Montréal: Montréal, 1971.) \$1.

Politics and Technology. By Roger Williams. Pp. 80. (Macmillan: London, February 1972.) 60p.

l'Engagement contains three addresses delivered at the fiftieth anniversary celebration of the Faculty of Sciences in Montreal University. Salomon discusses the social responsibilities of scientists as they have emerged. He remarks that when Bacon announced that "knowledge is power," he did not mention the difficulties implicit in this association. The idea of pure knowledge remained dominant. By the end of the Second World War the situation had changed fundamentally. In the war scientists associated with statesmen and strategists, and became established at the centre of politics. Science became limited to a sub-autonomy in society. The application of science brought abundance, and this required organization and planning. The quantitative caused a qualitative change.

The nature of modern science and the structure of modern society make them inevitable partners. The scientist's social duty to explain the implications of science to his fellow men, so that the best use can be made of it.

Des Marais discusses the recent evolution of the education of academic

scientists in Canada. There is no precedent for the present era, which is the consequence of the scientific explosion. To cope with it, it is necessary to revolutionize traditional notions of the organization of science and society. After a period of very rapid expansion consolidation is necessary. This involves the choice of priorities. These cannot be made without scientists, whose continued participation is now essential for the functioning of society.

Jean Dorst deals with the responsibilities of the ecologist. Many ecologists work in ivory towers. This attitude isolates them from the complicated problems of the biosphere. They should make their views known, and secure the support of the masses. They must inform the political authorities of ecological problems, and the urgency of their solution. They must create an ecological policy. He wants a new civilization in which the activities of man and the rest of the living world are carried on harmoniously.

Roger Williams's conclusions are that technology expands the politically possible, and there is a world-wide expectation of continually improving material standards. If technocracy is the newest mode of government, the older characteristics of muddle, incompetence, insincerity, injustice, and barbarity remain. Yet technological society is likely to seem increasingly pleasant to most of its members.

Williams has quoted 263 authorities in 54 pages. If his conclusions are not inspiring, he has provided students with a useful annotated bibliography.

J. G. CROWTHER

Separating Cells

Separations with Zonal Rotors. Edited by Eric Reid. (Wolfson Bioanalytical Centre of the University of Surrey, 1971.) (Distributed by the University of Surrey Bookshop, Guildford, Surrey.) £2.40.

SCIENTIFIC discoveries progress by leaps and bounds. The reason is generally the development of a new technique, of which the use of zonal centrifugation to separate biological materials is a case in point. The main advantages of zonal rotors over conventional types are that wall effects are avoided and that larger samples can be handled. This booklet is aimed both at the worker already engaged in zonal centrifugation and at the uninitiated not yet acquainted with the technique.

The first objective is undoubtedly achieved. The forty articles represent contributions from participants at a symposium devoted to this topic. There is a host of information, from

tables of physical constants for sucrose and Ficoll to detailed discussions about the suitability of methods for separating ribosomes, viruses, nuclei, mitochondria, lysosomes, plasma membranes, or whole cells. Useful, too, are the "do's" and "don'ts", reminiscent of advice on cookery or travel ("... US commercial sugar is to be avoided ..."), in spite of an occasional lapse into the near-incomprehensible ("It should not be thought that *all* lysosomes come under the umbrella of the GERL system ..."). The subject index is particularly welcome.

The second aim is less successful. The limitations imposed by the low production cost make it a somewhat bewildering manual. The grouping into seven sections is at best clumsy ("various elements including whole cells and non-hepatic subcellular organelles"), at worst incorrect ("particles not bounded by a membrane, especially ribosomes and viruses"). The success of any introductory book is, after all, largely a measure of the clarity of presentation.

The editor apologizes for providing glossy instead of vinyl covers, because of "adhesion problems". He should take heart from the fact that this symposium amply demonstrates the ingenuity of the contributors in solving a more fundamental problem—that of the adhesion between the components of living cells. C. A. PASTERNAK

Reptile Metabolism

The Temperature and Water Relations of Reptiles. By J. L. Cloudsley-Thompson. Pp. vi+159. (Marrow: Watford, Hertfordshire, 1971.) £2.50.

I THINK it is fair to say that reptiles have a fascination for most people but especially to biologists, most of whom work in an academic system that is largely organized about man and other mammals. There is a strong imaginative interest in the lives of creatures that may eat enough food in four days to keep them for the next 6–9 months, live through all their lives without drinking, that may withstand loss of 40 per cent of their body water, but may die when exposed continuously to "optimal" temperatures. Added to this is a particular sympathy for animals that have to go and sit in the Sun after meals to get warm enough to digest them, while we only have to find the heat to cook them. Reptiles have to achieve by ingenuity what their more sophisticated mammalian and avian colleagues are naturally equipped to do with their internal temperature-controlling systems. They do, by their behaviour, achieve a considerable degree of control of body temperatures at levels that

may be up to 30° C above air temperature, for example, by spending time at intervals acting as their own greenhouses and storing heat from the Sun. They may even sunbathe in water under a layer of ice.

The greater part (about three-quarters) of the book is about the temperature relations of reptiles; the rest about water relations, though the two are connected to some extent. It is a book that is packed with information, based on about 500 references, given, happily, with their titles (as well as 200 odd references not quoted in the text in a supplementary section). The references, in fact, have an interest of their own because more than 60 per cent of them come from the decade 1960–1969. If one counts them up by date from the year 1900 one finds the following numbers in successive decades starting with 1900–1909, 2, 5, 6, 30, 48, 86, 311. This is something like logarithmic growth with a doubling time of about eight years. Looking forward one can predict by the year 2000 about 1.5 papers a day on the topic of temperature and water relations of reptiles.

I find this an excellent thought and I hope the prediction may be correct; though I suppose I should add to this the hope that the papers will reflect an increase of interest and respect for reptiles, and not the results of research under contract to some future user.

R. D. HARKNESS

Crocodylians

The Last of the Ruling Reptiles: Alligators, Crocodiles and their Kin. By Wilfred T. Neill. Pp. xvii+486. (Columbia University Press: New York and London, 1971.) £7.50.

THE appearance of Wilfred T. Neill's important book, the first to deal comprehensively with crocodilian biology, will be most welcome to herpetologists, naturalists, and to all who share concern for an ancient and vanishing group of animals.

The work is divided into five parts, dealing respectively with legendary crocodiliana, biological classification and past history of the group, the natural history of the American alligator, and of the other living species. There is an admirable account of crocodilian fossil history, which has extended over more than 200 million years; of radiation in structure and habit, as seen in the diverse forms which existed in past ages — forms gigantic and minute, horned or almost toothless, maritime, freshwater and terrestrial; and of links established between the ancient and modern species. New light is thrown on the interesting question whether the

theodont ancestors of crocodiles were bipedal by a comparative study of bipedalism in modern lizards. The living crocodilians, of which there are some twenty-three species, receive separate and detailed treatment — taxonomic history, geographical range, habitat and ecological relationships, feeding habits and enemies, reproductive biology and social organization being among the topics reviewed.

Several chapters, and much space elsewhere in the book, are devoted to the exposure of fallacies and legends found in accounts by early natural-historians and uncritically accepted by later writers. Here the author's approach is unduly sceptical. In sifting truth from chaff he casts doubt upon many aspects of crocodilian behaviour that have been reliably observed and reported. For example, in his account of the Nile crocodile he regards as apocryphal the well-attested fact that the young call their parents at hatching time. He denies that the female excavates the nest, although observations of hundreds of nests on the Victoria Nile, Lake Rudolf and in Zululand have shown that successful hatching cannot take place without such assistance. The facts that the female subsequently conducts her brood to a refuge, and that the hatchlings remain gregarious and receive close and continued parental care, are dismissed as myths. In stating that there is scant evidence of territoriality in this species the author disregards work by Modha on Central Island, Lake Rudolf (though Modha's paper is included in the bibliography). Battles between adult crocodiles have been witnessed and filmed: but Neill says there is no convincing evidence that battles take place. Ignoring evidence to the contrary, he supports his statement by asserting that most mutilations found in crocodiles were probably received by hatchlings "which thereafter bore the signs of a narrow escape from some predator": in fact, the incidence of injuries in a wild population is known to increase progressively with age, and to be far higher among males than females.

Such faults, however, do not prevent this from being a fascinating book. The 152 text-figures add much to its value: they include useful maps showing ranges of the several species, and many original photographs—those of crocodilians mostly from Ross Allen's Reptile Institute, Florida. There is an extensive bibliography.

Neill doubts that any crocodilian species will persist in nature beyond the present century; and accordingly he suspects that his book will be the last to deal broadly with crocodilian biology. It is hoped that his prediction in both respects, will prove to be mistaken. HUGH B. COTT

CORRESPONDENCE

Science in India

SIR,—Dr V. H. Shah's suicide, and this is the second occasion that an Indian scientist has committed suicide, has exposed only the tip of an iceberg of the tremendous frustrations bright young scientists experience working in junior positions in some of the universities and research laboratories. The organization of research in India, both in the university and public research laboratories, is, as you have rightly pointed out, "too rigid, too hierarchical" and too authoritarian. Such an organization in any system, whether social, political or scientific, leads to the formation of narrow "yes men" cliques and results in demoralizing and stifling of independent minds. There would have been little progress in sciences and arts for that matter in the world without the presence of questioning minds. The present state of Indian science is not only not conducive to the progress of independent minds but demoralizing and frustrating, which in some cases leads to suicide while in others, if the person is adventurous enough to seek a position abroad, where he can work in a freer environment and have a chance to prove his abilities. This is the major reason, low salary scales, unemployment and under employment being other minor reasons, why large numbers of Indian scientists emigrate.

The Atomic Energy Commission Research Laboratories of India are an exception to this authoritarian organization, and this was due to the capable founder, Dr Homi J. Bhabha, who brought to bear his independent mind on the organization and attracted bright young scientists by way of encouraging an independent and non-authoritarian attitude to scientific research and better salary scales than anywhere else, including the Indian Administration Services (called the Indian Civil Service in the days of the British Raj). The then Prime Minister of India, Jawahar Lal Nehru, respected Bhabha for this and allowed him freedom from a lot of outdated bureaucratic rules still being observed in other institutions. Here is a case of a politician contributing to the progress of Indian science, and no Indian has done more in this field than Nehru. You maintain that a Cabinet Minister should not be the Chairman

of the Research Council. The presence of the Minister, or the Prime Minister, actually is a help, for as an outsider he can bring some independence and fair play to the present authoritarian organization. It is the organization of Indian science which is to blame for the present state of affairs and, unless there are radical changes in the outlook of those in the positions of authority, the presence of an independent outsider, such as a Cabinet Minister, or any public figure, will be necessary. I believe that the junior cadre of the Indian scientists is as good as anywhere in the world; the present organization, however, is so frustrating, and it is here that the changes are needed so that some of these bright scientists with respect for independence can come forward to lead Indian science and technology.

In the present circumstances, however, it is not easy to bring about a change since those enjoying authority will not like to see a reduction in their authority. The only way to change this is to start a discussion in independent scientific journals, such as *Nature*, and you have done a great service in initiating such a discussion.

Indian scientists, whether in junior or senior positions, face great challenges and can contribute to the betterment of the Indian society. But this can only be done by creating a proper environment for encouraging bright, independent young minds. I very much hope that well intentioned people, both in the Indian government as well as in research institutions and universities, will assert themselves to improve the present organization of the Indian science which leads to such tragedies as Dr Shah's suicide.

Yours faithfully,

K. C. TRIPATHI

16 St John's Way,
Hempton, Deddington,
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Military Sponsorship

SIR,—We have recently been circulated with details of a proposed Advanced Study Institute on proteins of the nervous system. Whilst we welcome such a development in principle, we were deeply disturbed to discover that its sponsoring agency was the North Atlan-

tic Treaty Organization (NATO). As is well known, NATO is primarily a military organization, and whilst in recent years its activities have ramified in a variety of directions, we must not forget what its primary mission is.

Sponsorship by a military organization of a scientific meeting must raise a number of questions. Are the deliberations of the meeting of use for military purposes? Is free scientific communication a permitted consequence of the meeting? What are the motivations and purposes of the sponsors?

In commenting on these questions, which have the gravest implications for participants in the Institute, we must note the following:

(1) Research on the mode of action of the nervous system at the biochemical level, and particularly on synapses and their related pharmacology, has been funded by military institutions in the USA, UK, West Germany, Australia, Canada and, doubtless, the USSR, on an increasing scale over the past two decades for its potential in the development of chemical weaponry. Weapons systems based on this research, and whose use would be a clear violation of international law, are currently stockpiled by a number of NATO countries, including, particularly, the US, and have indeed reportedly been used by the US in Vietnam.

(2) Frequently the military purposes for which research grants from Defence Departments have been given have not been revealed by the sponsors to participating scientists, who have accepted the grants believing them to have quite other implications. A recent case, at Stanford, has received extensive coverage in *Science* (175, 866; 1972).

(3) Free communication at a NATO summer school is rendered improbable because it is highly unlikely that scientists from the Soviet Union, Eastern European Countries, China, Cuba, or the Democratic Republic of Vietnam would be able to attend.

(4) Although we recognize that a "cultural" role is built into the terms of the NATO treaty, it is necessary to consider whether, in such cases as this, the cloak of scientific respectability is being used to lend spurious legitimation to a primarily military organization.

We have written individually to all

the named participants in the Study Institute, soliciting comments from them on these views, but would welcome the opportunity of opening the debate up within a wider section of scientific opinion, through your columns. Can we invite those readers of *Nature* who have views on this matter to communicate directly with us?

Yours faithfully,

JIM COHEN
JOHN HAMBLEY
JAVAD HASHTEROUDIAN
JEFF HAYWOOD
LES PEARCE
KEN RICHARDSON
STEVEN ROSE
ARUN SINHA
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Predicting Population

SIR,—There are two additional factors in the prediction of population besides those which were mentioned in John Maddox's article (*Nature*, 236, 267; 1972), which seem to me to be worth comment.

The first is that in educated and civilized communities, people's behaviour in reproductive as well as other respects is determined not only by their immediate and past environment as it is with most other creatures, but also with their expectations for the future. In consequence, coming events cast their shadow before on birth rates to an extent which is becoming increasingly important.

Arising out of this is the second factor which I would like to mention. This is rather like an extension of the uncertainty principle in physics. When Ehrlich, or Forrester and his computers, make convincingly unpleasant predictions concerning world population, these predictions will be read and understood by large numbers of people whose behaviour may thereby be affected.

Therefore even if the prophets have taken every possible existing factor into account, they cannot take into account the effects of their own predictions.

It is difficult to feed into a computer analysis the effects of knowledge of its own extrapolations on birth rates or pollution. It is, however, abundantly apparent that our responses to pollution and population changes are far more determined by their rates of change, and hence the direct extrapolations of their effect, than they are by the present magnitudes. Forrester explicitly rules this out in his computer calculations, and thereby, it seems to me, very reliably invalidates them.

This is not a criticism of the value of predictions; rather it is an explanation of where their value lies. A prediction which could not be modified by a change in our actions really *would* be useless.

Yours faithfully,

J. H. FREMLIN

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Obituary

Professor N. P. Buu-Hoï



PROFESSOR BUU-HOÏ, French and Vietnamese expert in medicinal chemistry and cancer research, died of a heart attack in Paris on January 28, 1972.

N. P. Buu-Hoï was born on June 15, 1915, in Hué, and is of the Royal Family of Vietnam. Partly because of the desire of his parents and partly because of his

own belief in the human value of science, he did not follow the traditional political career of his family, but instead took up research in biochemistry and medicine. He studied pharmacology at the University of Hanoi, and upon arrival in France in 1935 took degrees in physics and chemistry at the University of Paris. During the Second World War he volunteered as a pharmacist in the medical service of the French Army. From 1941 he held appointments on the research staff of the Centre National de la Recherche Scientifique (CNRS) where in 1960 he became director of research.

After 1941, he worked at the Institute of Chemical Physics under the late Professor Jean Perrin, then studied spectroscopy applied to organic chemistry, under the late Professor Ramart-Lucas at the Sorbonne. From 1945 to 1947 he was assistant professor at the École Polytechnique, and then went to the Radium Institute of the University of Paris as director of the Department of Organic and Medicinal Chemistry, where for more than twenty years he was the closest collaborator of the renowned cancerologist Professor Antoine Lacassagne, who himself died recently (see *Nature*, 235, 291; 1972). In 1960

he transferred his laboratories to a laboratory group at Gif-sur-Yvette, where he led a team of some 20 researchers while continuing his collaboration with Professor Lacassagne at the Radium Institute. From 1967, he also directed a second team of researchers at the CNRS Laboratories in Orleans.

The main research interests of Buu-Hoï were in the fields of biochemistry and pharmacology, but his exceptional gift as an organic chemist enabled him to apply the whole panorama of possibilities of synthetic chemistry to the search for new compounds of biochemical, biological, and pharmacological activity.

His scientific bibliography comprises over 1,000 papers and chapters in books, and records fundamental knowledge in chemistry, pharmacology and cancer research. From his laboratory stem drugs now in clinical practice as well as in experimental development, such as new thiourea derivatives for tuberculosis and leprosy, thyronamine for cardiac conditions, 6-aminochrysene for splenomegaly and cancer chemotherapy, and anti-rheumatismal agents and analgesics.

The study of chemical carcinogenesis represents the core of his scientific acti-

vities over the last 25 years, in collaboration with Lacassagne and numerous younger associates. This resulted in the discovery of a number of new classes of carcinogenic polynuclear, homocyclic and heterocyclic aromatics, the phenomenon of competition between active and inactive hydrocarbons in the production of skin tumours, and the role of various constituents of tobacco smoke in carcinogenesis and promotion. In the field of hepatic carcinogenesis, he studied the effect of various anticarcinogenic (*p*-hydroxypropionophenone) and promoting (reserpine) agents on tumour induction by the carcinogenic azo dyes and the nitrosamines.

In biochemical pharmacology Buu-Hoï, with Arcos and Conney in the USA, related the induction of microsomal oxidative enzymes by chemical agents and chemical carcinogens. Very recently, with Dr S. S. Epstein, he demonstrated an association between photodynamic and enzyme-inducing activities in polycyclic compounds.

With Saint-Ruf and Pham-Huu-Chanh he investigated the effect of tetrachlorodibenzodioxin, highly toxic and teratogenic contaminants in the herbicide 2,4,5-T, on several enzyme systems, and also established its fragmentation under electron impact.

In the area of medicinal chemistry, he found as early as 1946 that the development of tuberculosis bacilli is strongly inhibited by certain chemical families, notably the hydrazides. This observation was of importance some years later for Doagk in his discovery of the tuberculostatic drug, isoniazid. His research on *p*-hydroxypropionophenone led to the introduction into therapeutics of moderators of hypophyseal function.

Independently from R. Mayer in the United States, Buu-Hoï discovered the efficacy of the thioureas in the treatment of tuberculosis and leprosy. Treatment of leprosy patients in South Vietnam with 4,4' - diethoxythiocarbaniide showed this drug to be an active therapeutic agent in both lepromatous and tuberculoid leprosy; and a preliminary trial of 2-mercaptobenzimidazole in a small number of patients gave encouraging results in lepromatous leprosy. With Pham-Huu-Chanh he demonstrated the positive inotropic properties of thyronamine and its derivatives. More recently they described the cardio-stimulant and hypotensive properties of one of the *N*-substituted derivatives of the amphetamines, some of which also possess considerable potency as local anaesthetics. Professor Buu-Hoï received wide international recognition. He was honoured by several awards from the French and the Dutch Academy of Sciences, the French Academy of Medicine, the French Ministry of National Education, and the French League against Cancer. He was Com-

mander of the Legion d'Honneur and of the French Order of Public Health. Among others, he belonged to the Société Chimique de France, the Chemical Society (London), the Society of Heterocyclic Chemistry, and was a corresponding member of the American Association for Cancer Research and honorary member of the Medical Society of Vietnam and the Society of Medicine and Therapeutics of Argentina. In his native country, he had held a professorship and the post of director-general of the National Office of Atomic Energy. He served on several international scientific organizations, in particular as member of the board of governors of the International Atomic Energy Agency, and of the panel of experts for leprosy of the World Health Organization.

He was also on the editorial board of *Chemotherapy*, *Medicina Experimentalis*, the *Journal of Heterocyclic Chemistry*, the *Journal of Medicinal and Pharmaceutical Chemistry* among others. As a gifted linguist, he could lecture and write in many of the European and Asian languages.

In addition to his scientific and medical activities, Buu-Hoï was involved in public service for Vietnam and for France. Thus, in 1953, he was entrusted with a special mission to Asia by President Vincent Auriol, in an attempt to negotiate a ceasefire in Indochina; he also carried out several cultural missions to Germany for France. For his native Vietnam, Professor Buu Hoï served as science adviser to the late President Diem and, as director of the Atomic Energy Establishment of Vietnam, was instrumental in the development of an Atomic Energy Research Centre, including a nuclear reactor system in Dalat. He also represented the Republic of South Vietnam as ambassador to several African countries and, in 1963, to the United Nations. He was offered, and rejected, important political appointments because he felt he could serve humanity better as a scientist.

With all of his splendid reputation, his personal background, and the numerous honours accorded him from the world of science, medicine, and politics, Buu-Hoï was a modest gentleman, persuasive because he could document arguments with his wide-ranging factual knowledge; he was generous, charming and lovable. Science and humanity will miss Professor Buu-Hoï, the man and the scientist.

Professor J. J. C. Buckley

JOHN JOSEPH CRONIN BUCKLEY, Julien Courtauld Professor of Helminthology in the London School of Hygiene and

Tropical Medicine from 1946 to 1966, died on April 12 at the age of 67.

For more than 40 years Buckley gave his undivided attention to helminthology, and he edited the *Journal of Helminthology* from 1946 until his death. He will be remembered as the most self effacing, the most courageous and undoubtedly one of the greatest of a small group of parasitologists whose main scientific effort was to identify the helminths of medical and veterinary importance, to categorize them and to unravel their complex life cycles. He followed in the tradition of Kuchenmeister, Leukart, Bilharz, Looss, Cobbold, Manson, Fulleborn, Blacklock and Leiper.

When he joined Leiper's department in 1927 the life cycles of most of the common parasites of medical importance had already been worked out but there was one problem that remained unsolved: no one knew the vector of *Mansonella ozzardi*, a filarial parasite affecting several million people in the West Indies and South America. Buckley sailed for St Vincent and within a few months he had demonstrated the full development of the parasite in the midge *Culicoides furens*¹. This was the first of his numerous contributions to the knowledge of filarial infections in man and animals. From the West Indies he went to Malaya where in 1938 he found that *Culicoides* midges were the vectors of *Onchocerca gibsoni*, a parasite of cattle².

During the pre-war period many new foci of human onchocerciasis (river blindness) were found in Africa, and in many areas blindness rates of more than 10% were recorded. One of these was in Kenya in the "Valley of the Blind" and it was here where John Buckley demonstrated the development of the parasite in *Simulium neavei* and where he devised the first successful method of interrupting transmission by clearing the shade trees from the edge of the rivers, thus preventing the vector from breeding³.

After the war Buckley returned to Malaya and it was here where he produced the evidence for separating the parasites causing elephantiasis in man into two distinct genera, *Wuchereria* and *Brugia*⁴. He was, however, interested in the life cycle and pathogenicity of the parasites as well as with the taxonomic problems and it was in Malaya that he began the series of self-inoculation experiments that may have contributed to his early death. T. J. Danaraj and his colleagues in Kuala Lumpur had suggested that the common and disabling condition of tropical pulmonary eosinophilia might be caused by infection with filarial parasites of animal origin. Buckley was determined to put the hypothesis to the test and during the following two years he

inoculated himself on several occasions with *Brugia* parasites from animals. Each time he became quite ill and he developed the characteristic syndrome with fever, pneumonitis and a very high eosinophilia. In his classical papers^{2,5,6} describing these experiments the "human volunteer" remained anonymous and it was a feature of his modesty that whenever he lectured on the subject he never referred to his own rôle in these experiments. This was not the first time he had been the subject of a self-infection experiment; as early as 1931 he had demonstrated that the pig *Ascaris* was non-infective to man, and in 1933 he showed that although the hookworm *Necator suillus* was a distinct species it was capable of infecting man and that it could cause confusion in diagnosis.

In 1946, when Leiper retired, Buckley was appointed to the Julien Courtauld Chair of Helminthology in the London School of Hygiene and Tropical Medicine and he also succeeded Leiper as editor of the *Journal of Helminthology*. He edited the journal single handed without interruption up to the time of his death. It was very much a personal production, there was no editorial panel, he attended to every detail himself. He was in constant demand for his opinion on the identification and classification of helminths from man and animals and one job that he enjoyed was identifying the helminths collected from animals at the London Zoo.

For the last fifteen years of his life he was partially paralysed and he was rarely free from severe pain but he always produced the journal on time and he never missed a lecture. His students were unaware of his agony. He will be remembered with affection by thousands of postgraduate students from all parts of the world for his clarity of expression, his modesty, his

dry wit and, for those who could break through his barrier of reserve, for his unflinching help with difficult problems. Buckley was a deeply religious man but he was never sanctimonious and very few of his friends realized that he regularly attended mass. He sought no worldly honours but he was delighted when he was elected to receive the O'Connor award by the International Congress of Tropical Medicine in 1969 in recognition of his outstanding contribution to filariasis and only a few weeks before he died he was awarded the Doctorate of Laws by the National University of Ireland.

- ¹ *J. Helminth.*, **12**, 99 (1934).
- ² *J. Helminth.*, **16**, 121 (1938).
- ³ *J. Helminth.*, **25**, 213 (1951).
- ⁴ *Ann. Trop. Med. Parasit.*, **54**, 75 (1960).
- ⁵ *E. Afric. Med. J.*, **35**, 493 (1958).
- ⁶ *J. Helminth.*, R. T. Leiper Suppl., 17 (1961).

Announcements

International Meetings

June 27–30, **Chemistry at Interfaces**, Rovinj (Dr V. Pravdić, "Rudjer Bošković" Institute, POB 1016, 41001 Zagreb, Yugoslavia).

June 28, **Sampling in the Mineral and Metallurgical Processing Industries**, London (Editor, Institution of Mining and Metallurgy, 44 Portland Place, London W1N 4BR).

July 2–5, **Environmental Acoustics**, London (Meetings Officer, Institute of Physics, 47 Belgrave Square, London SW1X 8QX).

July 2–10, **South African Science Week**, Johannesburg (Secretary of Science Week, University of the Witwatersrand, PO Box 1176, Johannesburg, South Africa).

Reports and Publications

not included in the Monthly Books Supplement

Great Britain and Ireland

- PEP Broadsheet No. 536: Abortion and Contraception—a Study of Patients' Attitudes. By Jean Morton Williams and Keith Hindell. Pp. iv+62. (London: PEP, 1972.) 80p. [203]
- Questions About Plants. By Professor E. W. Simon. (An Inaugural Lecture delivered before The Queen's University of Belfast on 12 March 1969.) Pp. 15. (Belfast: The Queen's University, 1969.) [203]
- The Trend of Reading Standards. By K. B. Start and B. K. Wells. Pp. 80. (Slough: The National Foundation for Educational Research in England and Wales, 1972.) 70p. [203]
- Bulletin of the British Museum (Natural History). Entomology. Vol. 27, No. 2: A Taxonomic Review of the Species of *Cinara* Curtis Occurring in Britain (Hemiptera: Aphididae). By V. F. Eastop. Pp. 101–186. (London: British Museum (Natural History), 1972.) £3.40. [203]
- Fifth Annual Report of the Institute of Development Studies UK. Pp. 111. (Falmer, Brighton: Institute of Development Studies, University of Sussex, 1972.) [223]
- The Macaulay Institute for Soil Research. Annual Report for 1970/1971, No. 41. Pp. 79. (Craigiebuckler, Aberdeen: The Macaulay Institute for Soil Research, 1972.) [223]
- Loughborough University of Technology. Report to the University Court, 1970/1971. Pp. 110. (Loughborough: Loughborough University of Technology, 1972.) [223]

Other Countries

- US Department of the Interior: Geological Survey. Bulletin 1294-F: Cretaceous and Lower Tertiary Stratigraphy of the Gurabo and El Yunque Quadrangles, Puerto Rico. By Victor M. Seiders. Pp. iv+58+1 plate. 70 cents. Water-Supply Paper 1895-A: Summary of Data on Temperature of Streams in North Carolina, 1943–67. By Thomas H. Woodard. Pp. iii+39+1 plate. 75 cents. Water-Supply Paper 1899-F: Water Resources of the Big Black River Basin, Mississippi. By B. E. Wasson. Pp. iv+29+5 plates. \$4. Professional Paper 677: Post-glacial Lahars from Mount Rainier Volcano, Washington. By Dwight R. Crandell. Pp. iv+75+3 plates. Professional Paper 683-E: Early Miocene Nonmarine Diatoms from the Pine Ridge Area, Sioux County, Nebraska. By George W. Andrews. Pp. iii+17+2 plates. 50 cents. Professional Paper 687: Cataclastic Rocks. By Michael W. Higgins. Pp. iv+97. \$1.75. Professional Paper 703: Stratigraphy and Paleontology of the Revised Type Section for the Tahkandit Limestone (Permian) in East-Central Alaska. By Earl E. Brabb and Richard E. Grant. Pp. iii+26+2 plates. 50 cents. Professional Paper 750-D: Geological Survey Research 1971, Chapter D. Pp. v+227. (Washington, DC: Government Printing Office, 1970 and 1971.) [83]
- Smithsonian Contributions to Zoology, No. 112: Mimetic Relationships Involving Fishes of the Family Blenniidae. By Victor G. Springer and William F. Smith-Vaniz. Pp. 36. (Washington, DC: Smithsonian Institution Press, 1972. For sale by US Government Printing Office.) 50 cents. [103]
- Bibliographien des Deutschen Wetterdienstes Nr. 25: Agrometeorologische Bibliographie 1970. Bearbeitet von Maximilian Schneider. Pp. xx+217. (Offenbach a.M.: Selbstverlag des Deutschen Wetterdienstes, 1971.) [103]

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